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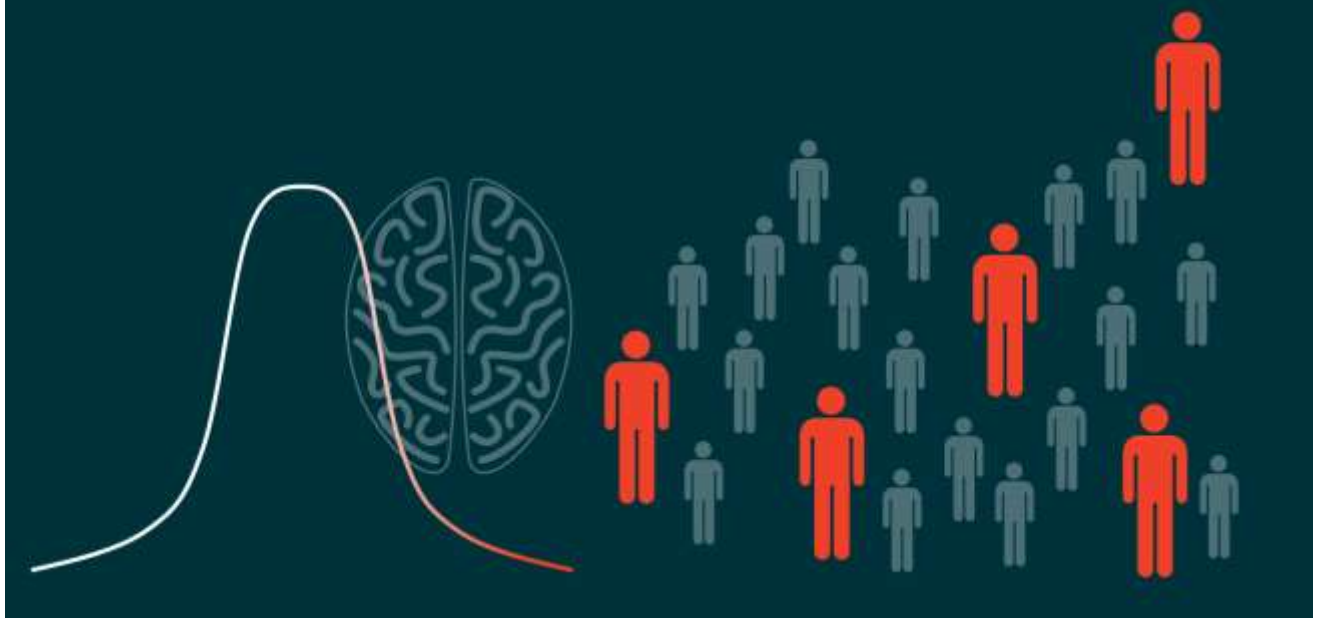
Polygenic risk scores in Alzheimer's disease
EXPLORING THE IMPLEMENTATION OF A NOVEL STRATIFICATION TOOL IN FLANDERS

List of abbreviations

ACCE	Analytic validity, clinical validity, clinical utility and ethical, legal and social implications
AChEI	Acetylcholinesterase inhibitor
AD	Alzheimer's disease
adORS	AD ORS
ADR	Adverse drug reaction
AE	Adverse event
APOE	Apolipoprotein E
APOE2	APOE E ε2
APOE4	APOE E ε4
APP	Amyloid precursor protein
Aβ	Amyloid beta
BRCA1	Breast cancer gene 1
BRCA2	Breast cancer gene 2
CAD	Coronary artery disease
CF	Cystic fibrosis
CSF	Cerebrospinal fluid
CT	Computed tomography
DM	Diabetes mellitus
DMT	Disease-modifying treatment
DTC	Direct-to-consumer
EFCAB11	EF-hand calcium binding domain 11
EMA	European medicines agency
FCSRT	Free and cued selective reminding test
FDA	Food and drug administration
GC/LC	Genetic counseling/Lifestyle change
GDP	Gross domestic product
GP	General practitioner
GWAS	Genome-wide association study
H3K9Ac	acetylation on histone H3 lysine
HCP	Healthcare professional
HD	Huntington's disease
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
INAMI	Institut national d'assurance maladie-invalidité
LDL	Low-density lipoprotein
MCI	Mild cognitive impairment
MRI	Magnetic resonance imaging
MRS	Methylation risk score
NFT	Neurofibrillary tangles
NMDA	N-methyl-D-aspartate
ORS	Oligogenic risk score
PET	Positron emission tomography
PGx	Pharmacogenetics
PRISMA	Polygenic risk scoring and deep Immunophenotyping strategy to master Alzheimer's disease
PRS	Polygenic risk score
PSEN1	Presenilin 1
PSEN2	Presenilin 2
PTRS	Polygenic transcriptome risk score

QALY	Quality-adjusted life year
QoL	Quality of life
RIZIV	Rijksinstituut voor ziekte- en invaliditeitsverzekering
SCD	Subjective cognitive decline
SNP	Single nucleotide polymorphism
TW	Transcriptome-based weighing
UK	United Kingdom
VLAIO	Flemish institute for innovation and Entrepreneurship
WTP	Willingness-to-pay
ZIN	Zorginstituut Nederland

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General introduction

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1. Introduction

Dementia is a widespread medical condition with severe outcomes and a growing incidence. Currently, it is estimated that **over 190,000 people in Belgium suffer from dementia, with Alzheimer's Disease (AD) being the most common cause**. The prevalence of AD is expected to double by 2025 (1).

Polygenic risk scores (**PRS**s) are gaining increasing attention in research and clinical practice. PRS has already shown its clinical applicability in cardiovascular disease and breast cancer. Therefore, the research project **"Polygenic Risk scoring and deep Immunophenotyping strategy to Master Alzheimer's disease"** (**PRISMA**) was set up under the auspices of the Flemish Institute for Innovation and Entrepreneurship (**VLAIO**). The project brings together a consortium of academic and industrial partners working on various aspects of PRS within the field of AD. This report presents the findings of an landscape analysis and early value model.

The report is structured as follows

| General introduction
| Part 1: Landscape analysis (methods, results, and discussion)
| Part 2: Early value model
| General conclusion

2. Alzheimer's disease

AD is a chronic neurodegenerative disease responsible for 60-70% of dementia cases. It is characterized by a gradual decline in recent memory, language, visuospatial drawing, concept formation, and problem-solving. Biological changes in the brain occur years before the first clinical symptoms emerge (2). **Mild Cognitive Impairment** (**MCI**) is an early stage of AD. It is characterized by a longitudinal decline in cognitive function without evidence of vascular, traumatic, or other medical causes. The key criteria distinguishing MCI from AD are preservation of independence in functional activities and lack of significant impairment in social or occupational functioning.

Typically, only **5-15% of people with MCI advance to the more severe stages of AD each year.** This is because age-related memory loss can resemble the gradually increasing forgetfulness associated with MCI (Figure 1). Approximately 50% of MCI patients remain stable after 5 years, and a minority may even experience a resolution of their symptoms over time (3). In patients with AD-associated MCI, cognitive decline progresses to include deficits in auditory and visual memory recall as well as auditory comprehension. In the later stages of AD, neurological, behavioral, and psychologic symptoms occur (4). The speed at which AD progresses is patient-specific and depends on factors such as age, other long-term health problems (e.g., diabetes mellitus (**DM**), cardiovascular disease), genetics, and gender (5). Differentiating between MCI caused by aging and MCI caused by AD is currently done through positron emission tomography (**PET**) or cerebrospinal fluid (**CSF**) function to test for amyloid beta (**Aβ**). The presence of Aβ is considered diagnostic for AD.
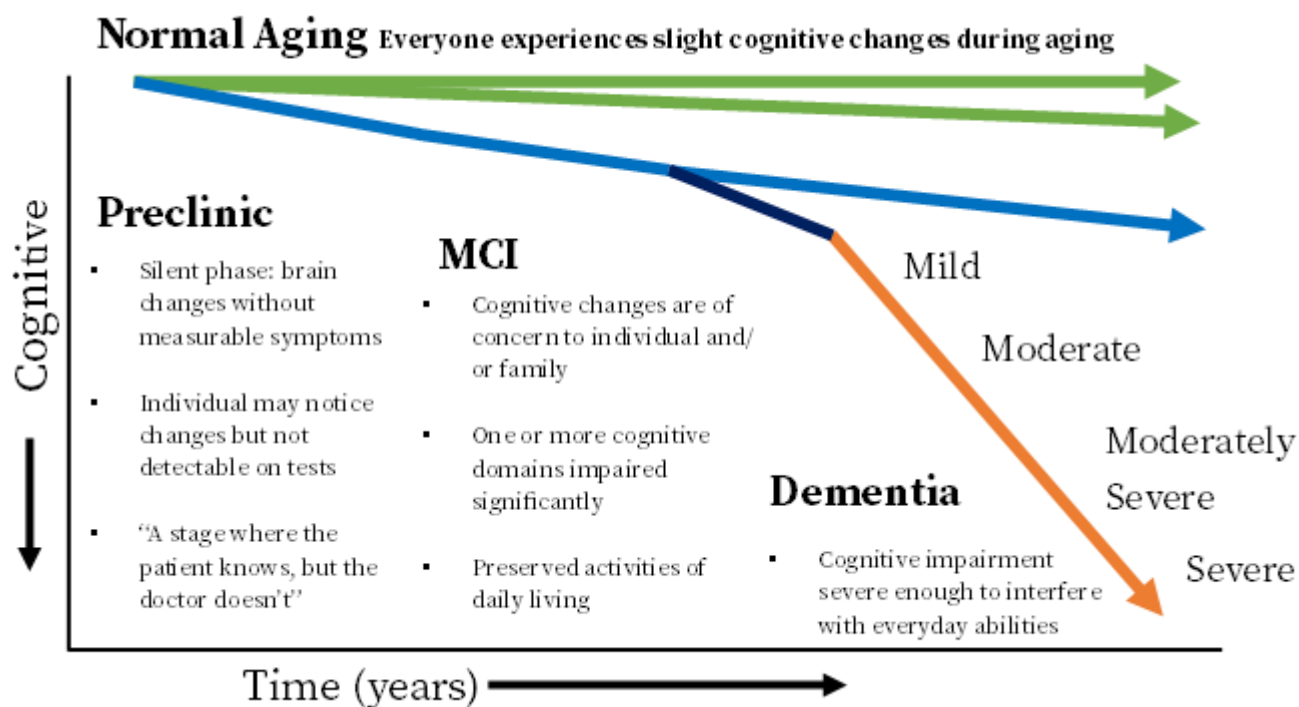
Figure 1. Progression from normal aging to Alzheimer's disease or another dementia, based on Alzheimer Centre Temple University (6). The green lines indicate normal aging, including limited forgetfulness. The light blue line indicates patients progressing to MCI due to aging yet not progressing to AD. The dark blue line indicates progression from MCI to AD, while the orange line indicates the later AD stages in which dementia gradually worsens. AD: Alzheimer's disease; MCI: Mild cognitive impairment.

2.1. Etiology

The etiology of AD is poorly understood, but **many genetic and environmental factors are associated with AD development** (7,8). In a small number of cases (<1%), AD is caused by mutations in a single gene: presenilin 1 (**PSEN1**), presenilin 2 (**PSEN2**), or amyloid precursor protein (**APP**). A mutation in any of these three genes follows an autosomal dominant inheritance pattern (7,8), leading to a 50% chance of inheriting the disease when one of the parents is a carrier. In this familial form of AD, symptoms usually emerge well before the age of 65 and are referred to as **early-onset AD**.

The most common form of AD is **late-onset AD**, in which symptoms occur in people aged 65 and older. Variations in genes (single nucleotide polymorphism (**SNP**)) have been identified with an increased risk for developing AD. These **SNPs increase or decrease the susceptibility to AD** but do not cause the disease. Variants in the apolipoprotein E (**APOE**) are the most well-known risk-increasing SNPs. Compared to non-carriers of the APOE E ε4 (**APOE4**) allele, heterozygous carriers of APOE4 have three- to fourfold increased odds of developing AD, and homozygous carriers have up to fourteenfold increased odds. Contrarily, the APOE- ε2 allele (**APOE2**) protects against AD development (9).

The SNP-based **heritability of late-onset AD is estimated to be between 58 and 79%,** indicating that there is also a role for non-genetic factors, which can be modifiable and non-modifiable (2). Modifiable risk factors include diet (obesity or DM) (10) and vascular risk factors (smoking, hypertension, hypercholesterolemia) (11), and can be improved with lifestyle adaptations (e.g., healthy diet, more exercise). Non-modifiable risk factors include old(er) age, head injury, metal exposure (Zn, Cu), immune system factors (10) and cognitive impairment or MCI (12).

2.2. Pathophysiology and neuropathology

The primary histopathologic lesions involved in AD are the presence of extracellular **Aβ plaques** and intracellular **Tau neurofibrillary tangles** (**NFTs**). The protein Aβ is derived from the sequential cleavage of APP and aggregates into oligomers, which are toxic to the neurons (13). In non-AD individuals, there is a balance between Aβ synthesis, re-uptake, and clearance, preventing the accumulation of Aβ and, thus, neurotoxicity (14). In the case of NFTs, alternative splicing of tau that typically forms soluble protein isoforms results in hyperphosphorylation, causing insoluble aggregates. (15). Decreasing the production of Aβ and tau prevents the protein's aggregation or misfolding, thereby neutralizing their toxic potential. Consequently, Aβ and tau are prime targets for disease-modifying treatments (**DMTs**) in clinical trials aiming to treat or prevent AD (13) effectively.

Aside from Aβ accumulation and aggregation of NFTs, a third central mechanism in AD development is chronic neuroinflammation (16), or brain inflammation. Neuroinflammation may protect the brain as a response to acute injury or infection. However, over-activation of the brain immune system plays a significant role in the progression of AD (16): it has been demonstrated that chronic neuroinflammation causes exacerbation of both Aβ and tau pathological processes, and as such, may serve as a link in the pathogenesis in AD (with elevated Aβ plaques increasing NFTs) (17).

2.3. Diagnosis

2.3.1. Alzheimer's Disease

Before the early 2000s, a **definite diagnosis of AD** could only be made through a brain autopsy after death. Post-mortem detection of pathological changes in the brain (e.g., Aβ accumulation) was the most common practice (18). Thanks to advances in research, lab, and imaging tests are now available to support detecting biological signs of the disease (biomarkers) in a living person. For example, abnormal accumulation of Aβ plaques and tau proteins in the brain can be visualized with PET (19). Aβ and tau proteins can also be quantified through a CSF examination. However, these investigations are expensive (PET) or invasive (CFS examination) (20). Therefore, a **suspected diagnosis of AD** can also be made based on clinical signs or neurocognitive batteries (21).

When AD is suspected, patients and healthcare professionals (**HCPs**) don't always feel the need for a definitive diagnosis, as **currently, only symptomatic treatment is available**, and a definitive diagnosis would not bring any additional benefit to the patient. Therefore, further steps are often not taken to confirm biological signs (i.e., Aβ plaques, tangles). In the case of early-onset AD, there is a higher need for a definitive diagnosis to exclude all other potential causes of dementia. As many general practitioners (**GPs**) are **unfamiliar with available detection and diagnostic possibilities** for dementia, and due to a lack of standardization in the diagnostic process, a lot of variation exists in the approach of GPs (22).

2.3.2. Mild cognitive impairment

As mentioned, AD is preceded by MCI. The diagnostic criteria for MCI include concern of patients or relatives regarding cognitive changes, but also an abnormal cognitive function in one or more domains or altered daily activity (23). Similar to the diagnosis of AD, there is no standard procedure for the diagnosis of MCI. One of the fundamental aspects of detecting clinical cues and making the diagnosis of MCI due to AD is a thorough interview with well-informed family members regarding the patient's history (24) and through cognitive testing. (25).

2.4. Management of AD

AD disease management includes **both pharmacological and non-pharmacological measures**. Furthermore, open communication between the physician, informal caregiver, and patient is required to

ensure the well-being of both the patient and caregiver(s). It should be noted that caring for someone with AD can pose a significant strain on relatives and can impact mental well-being (26). If necessary, support can be provided to the caregiver through psychoeducation or a network for caregivers.

2.4.1. Non-pharmacological treatment

Non-pharmacological interventions are interventions focusing on slowing down cognitive decline on the one hand (e.g., by increased movement, altered diet, or improved social interaction) and reducing neuropsychiatric symptoms such as anxiety, agitation, etc., on the other hand. Evidence for their effectiveness needs to be clarified (27).

2.4.2. Current pharmacological interventions

The treatments currently available for AD in Europe are acetylcholinesterase inhibitors (**AChEIs**) and N-methyl-D-aspartate (**NMDA**) receptor antagonists:

- **AChEIs**, such as galantamine, rivastigmine, and donepezil, are prescribed for mild to moderate AD symptoms (13). AChEIs attempt to reduce the breakdown of acetylcholine in the patient's brain by inhibiting the responsible enzyme (acetylcholinesterase). This enhances central cholinergic neurotransmission to slow cognitive decline during the first year of treatment (13).
- **NMDA receptor antagonists** such as memantine are prescribed for moderate to severe AD patients, aiming to maintain some daily functions for a more extended time by blocking the NMDA-mediated ion flux (28). They also lessen the dangerous effects of pathologically elevated glutamate levels seen in AD (13).

2.5. Drug development

In the last 20 years, no new drug for AD has been approved. Cummings et al. (29) provide an overview of 141 drugs that are currently being tested in clinical trials for the treatment of AD (on the index date of January, 1, 2023). Drugs in the AD pipeline address a variety of pathological processes: transmitter receptors, amyloid accumulation, synaptic function, and inflammation processes are the most common targets (Figure 2). Overall, DMTs, designed to slow disease progression, represent 79% of the drug development pipeline. Lecanemab, donanemab, and remternetug are the three most promising immunotherapies (**humanized monoclonal antibodies**) targeting cerebral Aβ-plaques. However, they are still controversial because the current safety and efficacy data do not support treatment in presymptomatic AD or moderate/severe AD patients. Furthermore, no supporting evidence indicates that these agents can stop or reverse cognitive impairment (30).

Recently, the Food and Drug Administration (**FDA**) approved aducanumab (2021) and lecanemab (2023). However, in Europe, the European Medicines Agency (**EMA**) has withdrawn the application of aducanumab and donanemab, and lecanemab, a drug from the same group, is still under review. Decisions on their approval are expected in early 2024 (31).
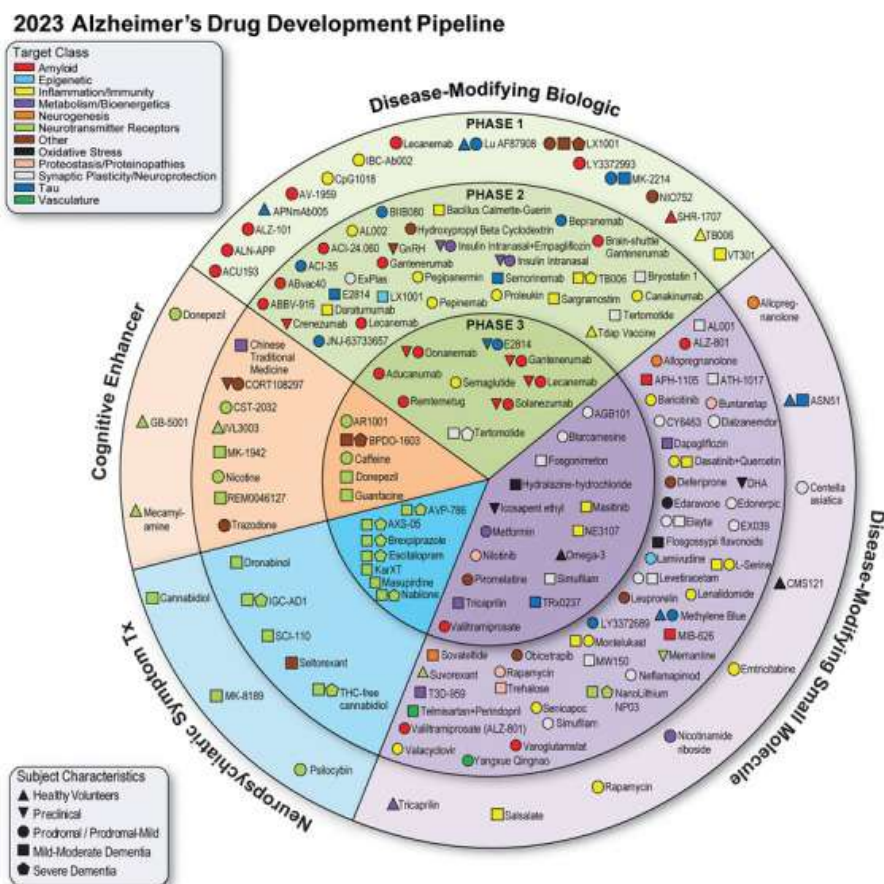
Figure 2. Agents in clinical trials for the treatment of AD in 2023 - as of the January 1, 2023 index date – reproduced from Cummings et al., 2023. AD: Alzheimer's disease.

Drug development for AD is not always that effective, including substantial financial and time investments, combined with high failure rates in preclinical as well as clinical trials (32). Furthermore, AD is a polygenic disease, resulting in a **complex and incompletely understood pathogenesis**. Therefore, developing new drugs is extremely challenging (33,34). New strategies such as **drug repurposing** are one of the main tactics researchers apply to identify potential treatments for AD (35). In drug repurposing, existing drugs are tested for other indications than initially approved. In the last decade, the number of publications regarding drug repurposing for AD has increased dramatically (36). In the AD drug development pipeline 2023 (29,37), 28% of the candidate therapies are repurposed agents. Most of the repurposed agents in 2023 are generic and funded by academic, advocacy, and philanthropic organizations.

2.6. Precision medicine

Because of the lack of success in the pharmacotherapy of AD, which can be related to the multifactorial etiology of AD, **precision-based combination therapy** targeting different factors simultaneously seems to be promising (38,39). Also, a better prognosis through early detection of AD biomarkers or brain imaging will enable early intervention. This could potentially prevent the deposition of Aβ-plaques, the formation of NFTs, and other manifestations of various irreversible symptoms of AD.

Precision medicine, or **personalized medicine**, is an approach to disease treatment and prevention that considers individual variability in genes, environment, and lifestyle for each patient. In personalized medicine, information from a patient's genetic makeup, molecular profiles, medical history, and other relevant data (e.g., family history) is used to make more accurate diagnoses, predict disease risks, and select

treatments that are most likely to be effective and safe for that particular individual. This approach aims to optimize patient outcomes by minimizing adverse reactions and treatment failures and reducing unnecessary interventions and expenses. The tailored medical decisions, interventions, and treatments are based on the unique characteristics of each person, rather than relying on a one-size-fits-all approach, known to benefit some, but not all, patients and often average results. Advanced technologies such as genomics, molecular profiling, and data analytics have significantly contributed to the growth of precision

3. Polygenic Risk Score

PRS can be used in personalized medicine to predict an individual's likelihood of developing a particular disease based on that individual's genetic profile. A PRS is developed by calculating a risk score based on genomic variants (SNPs) associated with specific population traits or conditions. APOE4 is the most significant genetic risk factor for the development of sporadic AD. It has been shown to increase Aβ deposition both in asymptomatic, MCI, and dementia stages of AD. However, variants in non-*APOE* genes have small effect sizes compared to APOE4, which is predominant. In isolation, these identified SNPs have limited use in predicting AD risks (40). Therefore, one single SNP does not predict someone's risk of developing a disease. Still, the combination of these genomic variances can potentially result in a score representing an individual's risk of developing a disease (40).

SNPs are derived from large-scale genome-wide association studies (**GWAS**), which identify correlations between specific genetic variations and the presence of certain traits or conditions within a population. PRS combines all this information to create a composite score that reflects an individual's overall genetic risk profile (41). Each PRS score can be put on a Gausse curve (Figure 3). Most people find their scores in the middle of this normal distribution curve, predicting an average risk for developing this particular disease. Individuals on the tail sides have a high (right) or low (left) risk.
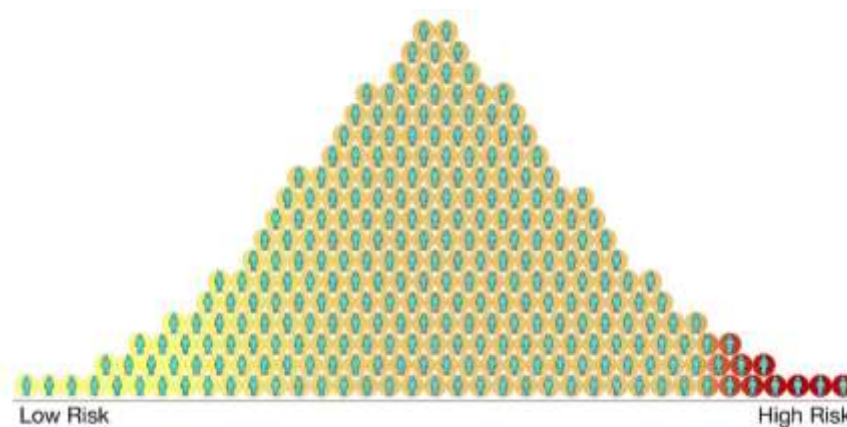
Figure 3. Representation of polygenic risk scores, reproduced from the National Human Genome Research Institute.

Consideration is required about the threshold used for the PRS score: lowering it improves sensitivity but reduces specificity, as shown in the value model, in which different scenarios with different PRS sensitivity and specificity are included. Increasing the threshold has the opposite effect. Therefore, an optimal threshold for SNP inclusion is still under investigation (40). As such, it is important not to overemphasize the impact of PRS (42).

Additionally, it is important to note that while PRS can provide insights into genetic predisposition, it doesn't guarantee that an individual will or will not develop a specific condition. Environmental factors, lifestyle choices, and other non-genetic influences also play significant roles in disease development.

Part I: Landscape analysis

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1. Objectives of the landscape analysis

PRSs have gained more research and clinical practice attention in the last decade. PRS has shown its usefulness in clinical practice in cardiovascular diseases and breast cancer. Within the PRISMA project, our goal is to explore the value and usefulness of a PRS for AD. One research partner focuses on the development of the PRS itself and is exploring different tools and methodologies to calculate the risk score. Other research partners are investigating the link between the PRS scores and AD symptoms and characterizing the behavior of immune cells (i.e., microglia) with a high score vs. a low PRS score.

This landscape analysis aims to explore the potential use cases of PRS in various contexts by conducting a literature search and analyzing examples from other disease areas. Additionally, it includes a critical reflection on the challenges and limitations of PRS in AD.

2. Methodology

A framework was developed to capture the different contexts in which PRS could be used. This framework covers the drug development process and the clinical journey, which aim to optimize AD management. The drug development process seeks to create new and improved treatments, whereas the clinical journey aims to manage the disease optimally, including optimizing pharmacological treatment.

With this framework as a theoretical backbone, an explorative literature search was performed to detect articles on using PRS within the specific context of the drug development process and the clinical pathway. Based on the articles found, an overview of the potential limitations and barriers to using PRS in each context was developed. Additionally, a critical reflection on the potential use in AD was made. This critical reflection was based on analyzing the available literature, internal discussions, and discussions with the other consortium partners with PRS calculation experience and AD clinical practice.

3. Results

3.1. PRS in AD

PRS could be used in research to facilitate **drug development** in AD and during the **patient journey** to support diagnosis and treatment (Figure 4). Using PRS in basic research might help better understand the disease and identify and validate new targets within the drug development process. Preclinical studies could use PRS to improve the efficacy of new drugs and to reduce toxicity. In clinical studies, PRS could facilitate the identification and selection of trial participants. For example, PRS might help to identify patients with MCI due to AD before the appearance of the first symptoms, as demonstrated in the value model. PRS could be used in the patient journey for risk prediction for AD development. A PRS score might also support the diagnosis of AD and aid in treatment decisions and prognostic predictions.
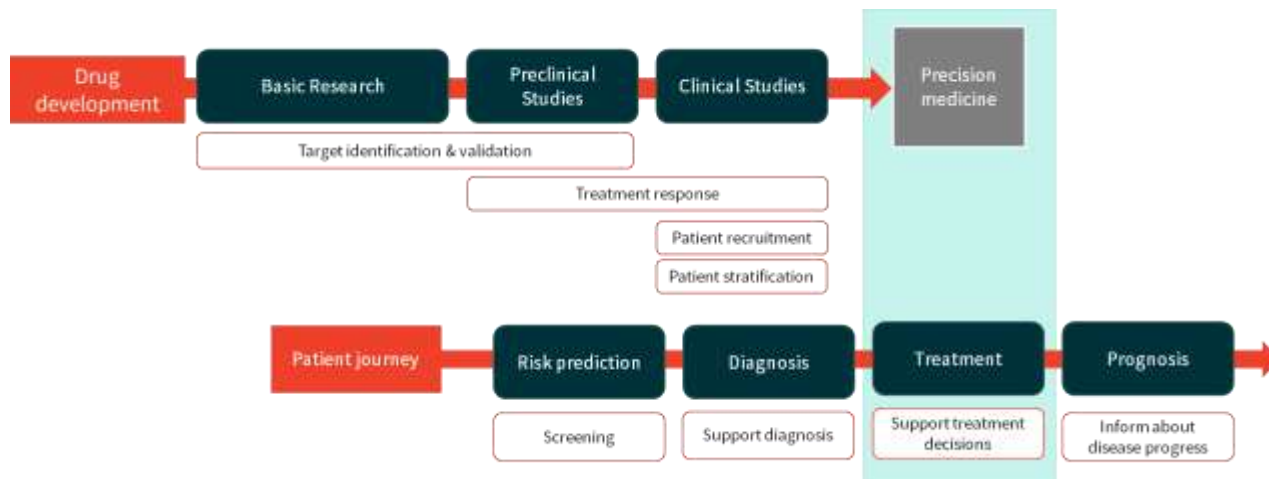
Figure 4. Drug development and patient journey in AD. AD: Alzheimer's disease.

Different PRSs, depending on the scope

PRSs are calculated based on the type and number of SNPs included. The type of SNP refers to its association with a phenotypical expression: SNPs might be associated with a specific trait or condition within a particular population, defined here as **genome-wide PRS** (Figure 5). For example, a PRS could be calculated based on SNPs associated with AD or cognitive decline.

A genome-wide PRS refers to a PRS including all SNPs (sufficiently significantly) associated with a condition or trait. Still, it is also possible to restrict the number of SNPs within the PRS to a specific set of genes, defined here as **gene set PRS** (Figure 5). Genes could be selected based on their biological function (e.g., their role in a specific pathway) or based on their expression profile within a particular cell type (e.g., the presence of a receptor on the cell membrane) (43):

In AD, gene set PRSs could be determined based on **genes associated with (patho)physiological pathways** such as amyloid precursor processing, immune response, protein localization, lipid transport and binding, and endocytosis (44). However, it can be challenging to determine with which gene a specific SNP is associated. The SNPs contributing to the bulk of the heritability are not near genes with disease-specific functions (44). Additionally, several research groups have shown that disease-associated SNPs are enriched in transcriptionally active regions, particularly in regions active in cell types relevant to diseases (44). Gene expression data might identify associations of specific cell types with traits (45). As many AD risk genes are specifically expressed in microglia and astrocytes, microglia AD PRS and astrocyte AD PRS have been developed (46).

To calculate a PRS, all SNPs associated with a specific trait or condition (genome-wide PRS) and linked to a subset of genes (gene set PRS) are included. However, SNPs vary in their predictive value for developing AD. In calculating a PRS, only the SNPs with sufficient (additional) predictive value are included.
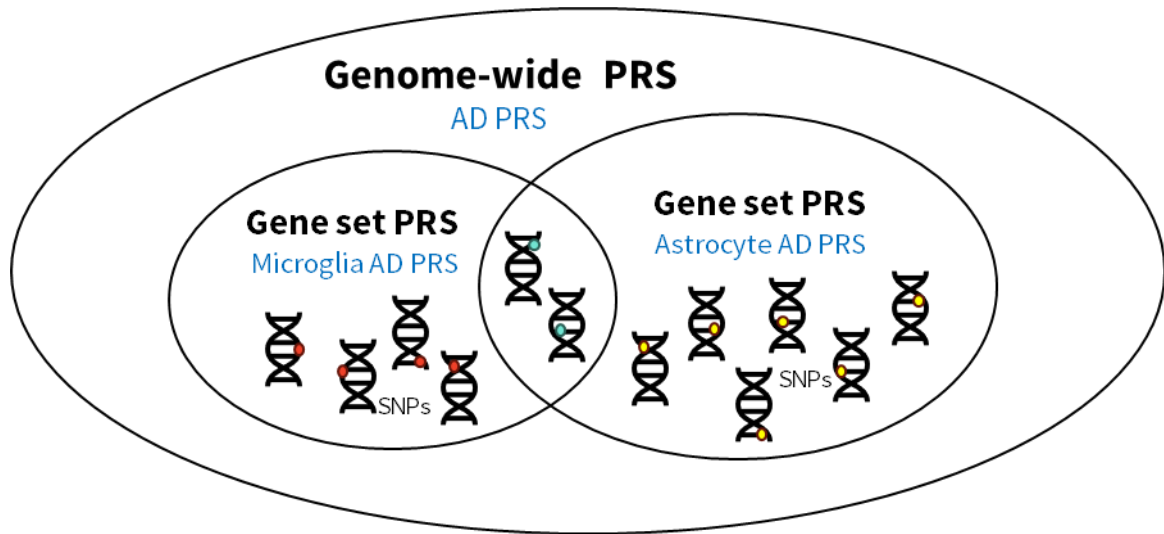
Figure 5. Different PRS scores depending on the scope. AD: Alzheimer's disease; PRS: Polygenic risk score.

3.2. PRS use in drug development

Drug development is a lengthy, costly, and high-risk process where it takes approximately 10 to 15 years for a new drug to get approval for clinical use (47). This process consists of three different steps: basic research, a preclinical phase, and a clinical phase (Figure 6).

- **Basic research** identifies mechanisms of action primarily involved in disease pathophysiology. It is an essential first step in discovering targets that could be of therapeutic interest.
- During **preclinical studies**, the efficacy and safety of potential treatments are tested in laboratory settings, *in vitro* and *in vivo*.
- **Clinical studies** are the last stage in drug development, wherein the drug is tested in people. Phase I trials focus on safety and the proper dosing, phase II trials focus on effectiveness and side effects, phase III trials compare the new treatment to existing treatments, and phase IV trials are real-world observational studies after the treatment is approved and available.
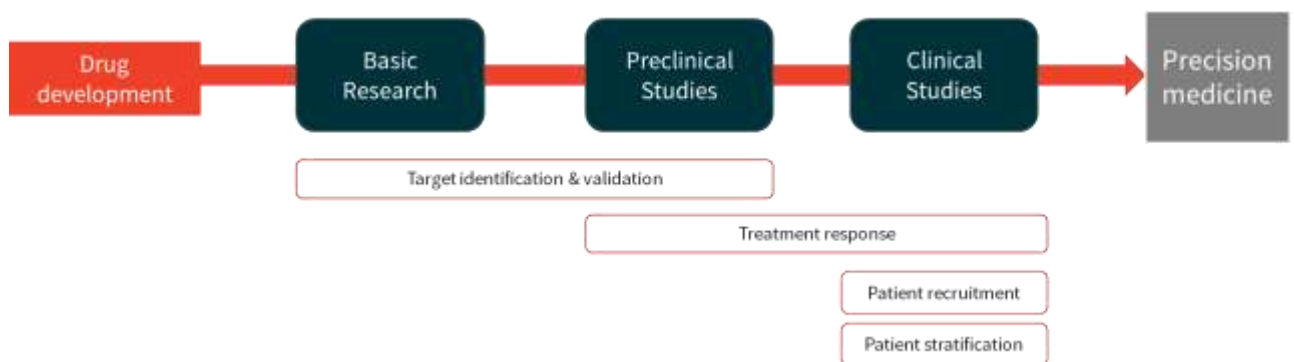
Figure 6. Drug development process and potential role of PRS. PRS: Polygenic risk score.

Many candidates identified during basic research don't make it to the market. For the drug candidates that have already advanced to phase I clinical trials, a failure rate of 90% is seen (48). Many fail to go through the complete clinical development process (47). Clinical trials for AD even show a failure rate of 99% (32). This failure is attributed to difficulties in patient recruitment as patients enroll only late in the AD disease process. Current research focuses on developing DMTs acting earlier in the disease process, which makes it challenging to recruit sufficient participants due to its late diagnosis. Linked to this late diagnosis is the

difficulty of obtaining informed consent for clinical trial participation: each participant must sign an informed consent.

PRS may aid in addressing the challenges faced in drug development by supporting **target identification & validation**, **understanding the treatment response**, **patient recruitment** to clinical trials, and **patient stratification**, which can be positioned in the continuum of the drug development process (Figure 6).

3.2.1. Target identification and validation

Genes and pathways linked to AD

During target identification, **genes of interest** are selected and linked to pathophysiological pathways in a particular disease (48). AD is a complex disorder involving many biochemical pathways (Figure 7). Potential drugs might be effective because they interfere in specific pathways but also because of many (still) unknown or unintended drug-target interactions, making it very challenging to identify new promising targets.
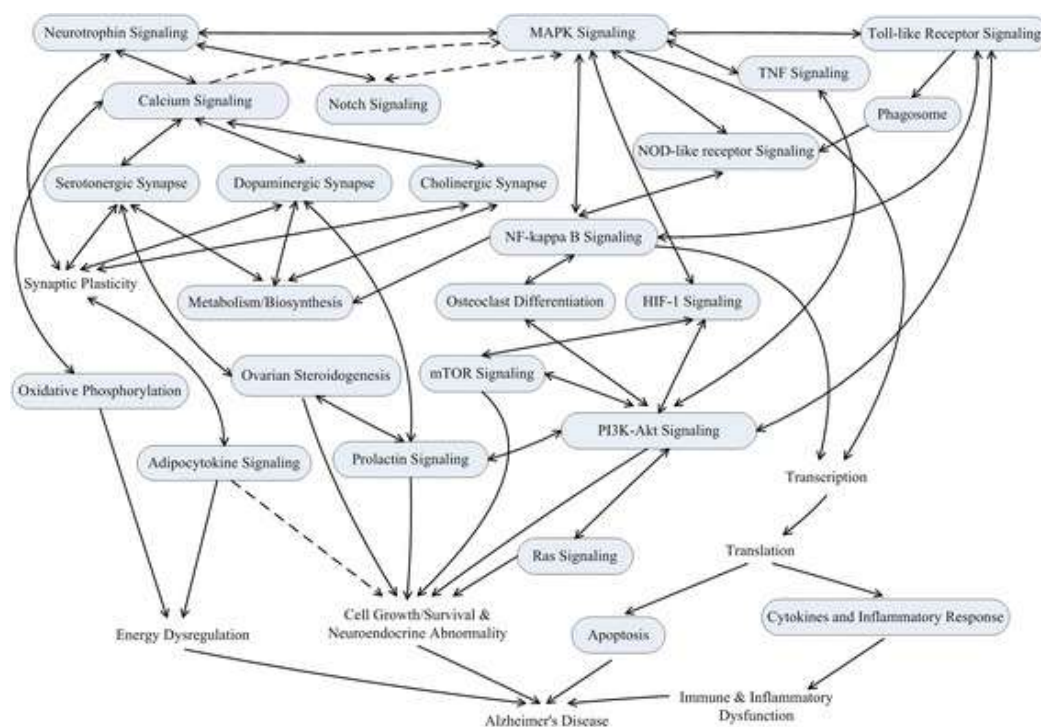
Figure 7. Main biochemical pathways related to AD, reproduced from Hu et al., 2017 (49). Main biochemical pathways related to AD. These major biochemical pathways involved in AD are connected based on their biological relations. AD: Alzheimer's disease.

In AD, **Aβ biogenesis** is one of the most important and known pathophysiological pathways. The APOE gene facilitates the transfer of cholesterol and phospholipids between cells. It is of particular interest as variations in the gene have an impact on the risk of developing AD (50).

- ApoE2 (5% incidence) is considered a protective variant against AD
- ApoE3 is the most common allele (75% incidence) and plays a more neutral role in AD
- ApoE4 (20% incidence) has an AD risk-determining effect and is the most substantial genetic risk factor for late-onset AD

Different studies suggest that this dominant gene variant (APOE4) contributes to AD pathogenesis through multiple pathways, including facilitated Aβ deposition, increased tangle formation, synaptic dysfunction, exacerbated neuroinflammation, and cerebrovascular defects (51–53). Because of its AD risk-determining

effect, the APOE4 polymorphism has become a promising target for eliciting pathophysiologic mechanisms and pathways, identifying individuals at risk for AD, and developing novel treatment strategies.

Besides target identification, **target validation** is also an essential step in drug development, such as drug repurposing, wherein drugs are used for indications other than previously defined and approved. These drugs need to be reinvestigated for the novel indication; depending on the case, the process reinitiates from the first step of drug development or in a later stadium.

The role of PRS

Genome-wide PRS includes all SNPs significantly associated with a condition or specific trait. A gene set-specific PRS restricts the number of SNPs to a particular set of genes. These gene-set-specific PRSs might provide new insights into the importance of specific pathophysiological pathways. However, **selecting genetic information** automatically results in an inability to capture the whole genomic fingerprint of a person since the PRS won't cover all traits (53–55).

Next to gene-set-specific PRS, SNPs showing a significant association with a condition or specific trait could also be an interesting target for drug development. However, SNPs that contribute to the bulk of the heritability in AD are far from genes with disease-specific functions, making it more challenging to link them with pathophysiological pathways. Additionally, even if inheritance of genetic factors might take up to 80% of AD, environmental and lifestyle factors play a role and should be considered (56).

PRS only accounts for the genetic component or trait, resulting in a static risk score, and does not consider these **environmental and lifestyle factors**. However, people's habits and behaviors significantly impact their health and well-being. A healthier lifestyle can reduce the risk of developing chronic diseases such as AD and improve overall quality of life (**QoL**) (57). Additionally, PRS calculations assume a **linear and static relationship** with the disease. However, in complex diseases such as AD, this is not always the case: many interactions cause non-linear effects, and the disease is dynamic in time. PRS models could not account for all these complexities and must be combined with more dynamic measures such as biomarkers, transcriptomics, and epigenetics.

Biomarkers

To account for the more static character of PRS, PRS could be used with **biomarkers** such as cognitive markers, CSF markers, and neuro-imaging markers, which are more accurate since they are dynamic diagnostic measures (40,58). Some of these biomarkers (neuroimaging) remain dynamic even after disease onset which can aid in monitoring the disease progression even at severe disease stages . In contrast, a PRS score remains unchanged/constant.

Studies revealed that **Oligogenic risk scores (ORS)** for AD might better predict disease risk using an optimized list of relevant genetic risk factors (59). Whereas PRS is derived from the weighted scores of GWAS significant SNPs, AD ORS (**adORS**) uses genes strongly associated with neuroimaging biomarkers to predict high or low risk of disease and the likelihood of progression from MCI to AD. APOE and EF-hand calcium binding domain 11 (**EFCAB11**) are the top genetic contributions.

Compared to conventional PRS, adORS improve the prediction performance, risk-based stratification of patients, and interpretability of genetic factors contributing to risk. The genetic heterogeneity of AD was also better represented with adORS. Though further studies are necessary, adORS are potentially interesting and can aid in developing treatments for AD.

Transcriptomics

As PRSs capture the variants in the genome, transcriptomics analyses how that DNA is expressed as proteins or other molecules. In basic research, **transcriptome** profiling aims to give insights into altered pathways related to AD (54). Combining PRS with transcriptomic data might provide new insights. A transcriptome-based weighting PRS (**TW-PRS**) can be created by mapping expression weights in each gene to SNPs in the gene, which were applied as additional weights in calculating the PRS (60). Adding expression weights of brain regions critical to AD progression enhanced the performance of conventional PRS.

Based on the concept of PRS, a polygenic transcriptome risk score (**PTRS**) can be calculated based on predicted transcript levels rather than SNPs (61). PTRS has shown a higher predictive score than PRS and has the significant advantage of improving the portability of PRSs across ancestries.

Epigenetics

BOX 1.1. Epigenetics

Epigenetics is defined as "making structural and biochemical changes in chromatin without changing the DNA sequence, and then regulating the expression of related genes, thus affecting various physiological and pathological processes." (Wang et al., 2019; Li, 2021)

PRS can also be combined with epigenetic data, as epigenetics can regulate the expression of related genes. Epigenetic changes have been observed in AD (62). DNA methylation, histone modification, and non-coding RNA changes are examples of epigenetic changes in AD. Epigenetics has been shown to control the transcription of genes related to cell differentiation, learning, and memory and has emerged as an important regulator of development and aging (63–68), the most significant risk factor for AD. However, it is not yet known whether they are a cause or a result of AD, as well as their exact role in pathogenesis.

A PRS for AD has been shown to be correlated with many chromosomal regions decorated with acetylation on histone H3 lysine (**H3K9Ac**) (69). More specifically, an increase in histone acetylation was observed in individuals with a higher genetic risk for dementia due to AD, which might impair transcriptional fidelity and advance the molecular age of the brain.

The concept of PRS has spread to epigenetics, particularly DNA methylation, to create methylation risk scores (**MRS**) (70). Epigenetics involves altering gene expression without changing the genetic code through DNA methylation and histone modification processes. MRS considers the methylation status at multiple genome locations. Unlike the genetic variants used for PRS, epigenetic markers for MRS change throughout life and are influenced by genetic and environmental factors. In this way, MRS may incorporate genetic factors, environmental exposures, and their variation over time. However, there are still many uncertainties to the ability of DNA methylation to aid in lifetime or long-term risk prediction. Combining MRS with clinical information may allow a greater understanding of a patient's risk than PRS (71).

3.2.2. Treatment response
Toxicity and optimal dosing

Before undergoing clinical trials, it is crucial to examine the **efficacy of a drug** by conducting toxicity and optimal dosing testing. In laboratory studies, researchers evaluate the safety of potential drug candidates using *in vitro* and *in vivo* models to enhance the desired clinical response and minimize the potential toxicity of the studied drug (72). Toxicity is a significant endpoint of potential drugs in the drug development process, which could lead to clinical trial failure.

Pharmacogenomics can aim to decipher the role of genetic variants on drug efficacy and drug toxicity. Investigation of the genetic profile might help, as clinical evidence shows significant variability in the response to pharmacological agents between patients (inter-individual variability). Thus, the genetic profile can majorly impact drug response (73). Pharmacogenomics can also aid in defining the optimal dosage of a drug and narrowing down the therapeutic index. An individualized dosing approach will accelerate the drug development process, ensure dose optimization, and increase the chances of positive clinical outcomes (73).

Adverse drug reactions

In clinical studies, its efficacy is investigated in patient versus control groups. Herein, adverse drug reactions (**ADR**s) and adverse events (**AE**) are studied, respectively described as unintended, noxious responses to a medical product and untoward medical occurrences after exposure to a medicine (72,74).

Not only the ADRs to one specific drug but also the interactions with other drugs need to be investigated. The simultaneous administration of multiple drugs, called **polypharmacy** (75), is widespread among the elderly and also contributes to an increasing susceptibility to toxicity (ADR as well as AE). These **drug-drug interactions**, together with underlying **comorbidities** of the patient, can potentially influence the drug response of the investigated drug, making it difficult to isolate the effect of one single drug (72). Therefore, polypharmacy complicates investigating the causal relationship between a single drug and its treatment response. Investigating **genes linked to a person's individual drug reaction** might prevent failures in later clinical trials.

Pharmacogenomics is important in avoiding and minimizing these poor treatment responses by identifying rare mutations that might result in a higher risk of poor outcomes. Examples are identifying allelic variations of genes involved in drug elimination, such as the cytochrome P450 family (76), impacting the drug response regarding efficacy and toxicity (72). It aims to ensure maximum efficacy with minimal adverse effects, evolving towards personalized medicine in which drugs and drug combinations are optimized for each individual's unique genetic makeup.

The value lies in the ability to select (and exclude) patients that will respond poorly to the drug, allowing (later) clinical trials to include fewer patients to assess similar effects.

BOX 1.2. Pharmacogenomics vs. pharmacogenetics

Pharmacogenomics deals with the simultaneous impact of multiple mutations in the genome that may determine the patient's response to drug therapy, whereas pharmacogenetics (**PGx**) is the study of genetic causes of individual variations in drug response.

The role of PRS

PRSs are, in this case, a valuable tool to explore the genetic liability of treatment responses (77). Introducing patient-level PRS to PGx (PRS-PGx methods) might seem very promising because PRS reflects the genetic predisposition for a specific phenotype and has a higher capacity to predict risks of complex diseases and health-related conditions (72). This is done by considering the minor impacts of many variants from genome-wide scope in a single numeric index.

Identifying patients who will respond to a specific treatment can be done by using these combined PRS-PGx methods, aiming for the best response and efficacy of the drug (78). Herein, PRS could support the **assessment of toxicology profiles** and **prediction of drug responses**, which may aid in reducing AEs during later clinical studies. Besides, it could improve the cost and efficiency of clinical trials by identifying individuals based on a **higher risk of disease** or an **increased probability of benefit** (79).

Therefore, the potential impact of using PRS as a tool in pharmacogenomics is very promising, accounting for the complex interplay between the polygenic nature of a **patient's genetic predisposition** and its **drug response**. However, their exact relation remains largely unknown because studying safety and efficacity endpoints of the treatment in clinical trials is more challenging.

In the case of DMT, a gene-specific PRS might provide new insights into patients' toxicology and potential drug responses. This information is important during the investigation of treatment responses in (pre)clinical trials.

3.2.3. Patient recruitment to clinical trials

Initially, in AD clinical trials, patients of interest were the ones who were likely to progress rapidly, as this facilitated assessing the impact and efficacy of a new drug within a limited time frame (80). Additionally, patients were only enrolled late in the disease process as patients are mainly diagnosed later in the disease process (79,81). Treating patients in later phases of the disease might decrease the efficacy of the product under investigation as the disease has been ongoing for many years (brain changes already occur decades before the first symptom onset (asymptomatic phase). Additionally, the patients can only be followed up for a shorter time.

Consequently, clinical trials, even those with high potential, fail to achieve clinical and/or statistical significance due to too late and little patient enrollment. This is also the case for DMTs, such as an antibody that clears Aβ plaques from the brain (79).

Prognostic enrichment could be of interest to increase event rates (i.e., the number of trial participants who will develop AD) and earlier enrollment of patients in clinical trials (79).

BOX 1.3. Prognostic versus predictive enrichment

Prognostic enrichment aims to increase the statistical power of a trial by increasing the proportion of patients likely to demonstrate disease onset or progression. The use of prognostic enrichment thereby allows decreasing sample size and costs while maintaining statistical power. Predictive enrichment aims to enroll participants more like to have an outsized benefit from the trial intervention.

Therefore, it might be helpful to have methods detecting individuals at risk for AD prior to symptom onset to support early detection of clinical study participants. Especially as the DMT research focuses on slow disease progression, early diagnosis and recruitment are of utmost importance (82). The Free and Cued Selective Reminding Test (**FCSRT**)[1] can help identify patients with an elevated risk of developing AD dementia (83), thereby enriching the potential clinical trial population with individuals with prodromal AD who are likely to progress during the study. These individuals are particularly of interest to prove the efficacy of the investigated DMT targeting the early stages of AD. This neuropsychological FCSRT test is currently used as an inclusion criterion in several sponsored studies (phase III trials of crenezumab and gantenerumab).

The role of PRS

PRS, being a risk score, might play an important role in prognostic enrichment as it allows the identification of patients in whom the development of AD is more likely and, as such, aids early diagnosis of AD patients and enrollment in clinical studies. This earlier enrollment by using PRS can result in an increased **population**

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[1] *The FCSRT allows to identify prevalent dementia, predict future dementia, identify patients with MCI destined to develop AD, and distinguish AD from non-AD dementia.*

size in AD clinical trials and facilitates a **longer follow-up** of patients. (84). PRS is already successfully used for early diagnosis of other pathologies such as breast cancer (85).

Post hoc analysis of several clinical trials suggests that PRS holds promise as a powerful enrichment strategy since individuals with the **highest PRS demonstrated the most significant benefits**. This benefit was related to both prognostic and predictive enrichment. Consequently, future clinical trials could successfully demonstrate benefits with substantially fewer participants using a PRS, predicting the enrichment in advance (79,86,87). Further research is needed to determine whether 'pathway-specific' PRS scores may provide more reliable predictive enrichment (88,89).

3.2.4. Patient stratification

Patient stratification is the division of a patient population into distinct subgroups based on the presence or absence of **particular disease characteristics**. It plays an important role in drug development as it might help to enrich clinical trial populations, which is challenging in AD (90). AD is a heterogeneous, multifactorial disorder with various pathobiological subtypes showing different forms of cognitive presentation, currently referred to as the Alzheimer spectrum or continuum (91). In addition to four major subtypes based on the distribution of tau pathology and brain atrophy (typical, limbic predominant, hippocampal sparing, and minimal atrophy), several other clinical variants (non-amnestic, corticobasal, behavioral/dysexecutive, posterior cortical variants, etc.) have been identified. These heterogeneous AD variants are characterized by different patterns of key neuronal network destructions, particularly the default-mode network responsible for cognitive decline (91).

The stratification of patients on genotypic and phenotypic variability is even more challenging in the prodromal stages of AD due to the difficulty of early detection of AD. Because current DMT treatments in the AD pipeline mainly target these earlier stages of AD, robust stratification methods are necessary (80). This involves excluding people who are ineligible for DMTs based on a combination of cognitive and functional assessments, genetic risk factors, demographic or lifestyle factors, and AD pathology (CSF and PET imaging biomarkers, magnetic resonance imaging (**MRI**)) (80). However, a difference between static and dynamic factors needs to be made.

The role of PRS

PRS is a powerful tool that might aid in disease risk stratification and prognostication in common complex diseases early in the disease process. It is already used in clinical practice in ophthalmological diseases. The ideal clinical use scenario is in conditions in which early intervention will alter the natural history of the disease and reduce morbidity or mortality.

Combining large numbers of these genetic variants into PRS has recently shown clinically meaningful risk prediction across several common diseases. PRS have the potential to translate the discovery of common risk variants into individualized disease risk prediction and prognostication and may enable targeted treatments. However, a PRS allows disease risk stratification but is never a diagnostic tool: its clinical utility is best achieved when combined with demographic and/or clinical factors usually evaluated in routine clinical risk assessment (92).

3.3. PRS use within the AD clinical journey

BOX 1.4. The clinical journey

The clinical journey describes the different moments within a patient's life in which PRS can support clinical practice, as opposed to the clinical pathway, which is the trajectory a patient follows from first disease awareness over diagnostic tests, treatment (if available) and end stage disease. The clinical journey includes risk prediction, diagnosis, treatment and prognosis. Which PRS is best suited depends on the specific aim and step within the patient journey (Figure 8). For example, phenotype PRS can play a role in risk prediction, diagnosis, and prognosis, but is unlikely to be valuable in treatment decisions.

Figure 8. Involvement of different PRS scores in the patient journey. PRS: Polygenic risk score.

3.3.1. Risk prediction

About 35% of the lifetime risk of dementia (due to AD and other causes) is modifiable by factors such as education, nutrition, exercise, healthcare, and (social) environment (93). As there is currently no treatment for AD, predicting AD risk before disease development is vital in disease prevention. PRS can be helpful in this regard. For example, in breast cancer, PRS helps to provide a more personalized risk assessment and to identify women at higher risk for breast cancer. This practice enables the implementation of stratified risk screening programs (85). Similarly, PRS could guide preliminary screening by detecting patients who are genetically (more) susceptible to the development of AD (55). Three different asymptomatic target populations for PRS assessment can be defined (Figure 9):

1. **Population risk prediction via general screening at birth**: a scenario where all newborns get screened for AD, so their risk of developing the disease is known from birth.
2. **Presence of significant risk factor as an indicator for preliminary screening**: a scenario where individuals with a substantial risk factor for AD development get screening to determine their risk prediction.
3. **Hereditary burden as an indicator for preliminary screening**: a scenario where

individuals with relatives with AD receive screening to determine their risk of AD.
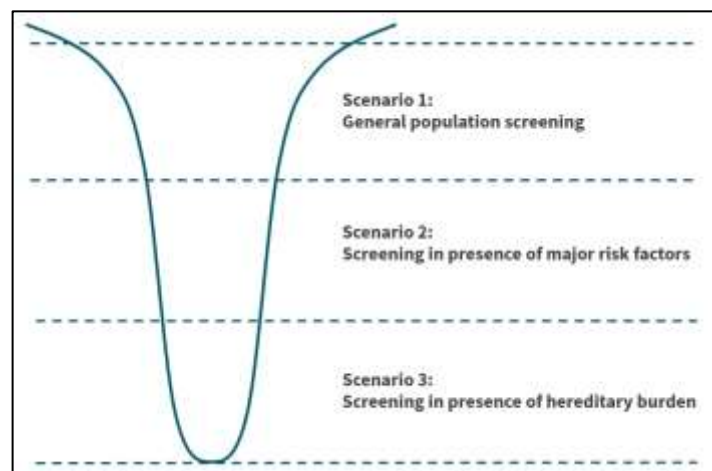

Figure 9. Asymptomatic screening scenarios for AD using PRS. AD: Alzheimer's disease; PRS: Polygenic risk score.

Population risk prediction via general screening at birth

Screening the whole population at birth can predict a risk of developing a particular disease throughout life. In Flanders, screening is offered for all newborn babies for 18 congenital diseases between the third and fifth day after birth to install appropriate treatment timely if required (94). However, this screening program is driven by the criteria of Wilson and Jungner:

1. Screening is implemented for an important health problem for which the natural history is well understood.
2. The disease is detectable in an early stage.
3. An acceptable test is available in this early stage.
4. For which early treatment is beneficial and available (95).

In these cases, early identification provides the opportunity to initiate treatment before irreversible changes, such as neurological damage, have occurred, to slow down disease progression, or to increase the chances of recovery.

Relevance for PRS in AD

Population-based PRS screening would allow to gain insight into an individual's AD risk from early on in life and acquiring an AD-protective lifestyle (Management of AD). This is not done in current practice, not for AD or other polygenic diseases.

Implementation in clinical practice

From a purely practical point of view, the blood test at birth (Guthrie test) currently practiced as part of population screening for congenital diseases in newborns, could be expanded with screening for AD using PRS. There would not need to be any adaptations to the current blood sampling protocol, only requiring additional tests. The procedure for neonatal screening would not need any adaptations towards using PRS in clinical practice. However, before implementing this practice, some ethical questions should be addressed (Considerations).

Presence of significant risk factor(s)

PRS screening in patients with significant risk factors is a strategy proposed by Mavaddat et al. (96) for the identification of patients at high risk for estrogen receptor-specific breast cancer not caused by rare monogenic mutations such as BRCA1 and BRCA2[2]. In this study, PRS allowed for the stratification of women according to their risk of developing breast cancer, which in turn holds promise for targeted breast cancer screening and prevention programs (96), e.g., more regular mammography or earlier screening compared to the average eligible population for BC screening in Belgium (women between ages 50-69).

Relevance for PRS in AD

Similarly, PRS may improve the detection and stratification of high-risk patients when used in patients with one or more risk factors and adapt further steps in diagnostics or treatment based on the patient's total AD risk. For example, PRS screening in patients aged 65 or older with cognitive impairment may improve referral and further diagnostic testing (Impact of PRS within the diagnostic process). Ideally, modeling all risk factors and/or predictors – cognitive impairment, high PRS, family history, and/or other risk factors – may allow for a near-certain risk prediction of AD development. Machine learning risk prediction models (not including PRS) for AD development are coming (97).

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[2] BRCA: Breast cancer gene 1 and Breast cancer gene 2.

Implementation in clinical practice

Implementation in clinical practice would require offering PRS testing in all patients with one or more risk factors for AD and, as such, modeling the risk based on the variable presence and severity of these major risk factors to determine in whom to perform PRS screening.

Hereditary burden as an indicator for preliminary screening (presence of family history of disease)

In Belgium, children and adults can get tested for hereditary diseases such as Huntington's disease (**HD**). Individuals who have a parent or sibling with HD are at-risk carriers, have a fifty percent chance of carrying the pathogenic gene (98), and are therefore eligible candidates for screening. They can receive an assessment of their carrier status of the genetic abnormality for HD using a presymptomatic genetic test (99). It allows people with HD (carrier status) to participate in clinical trials or scientific research that might benefit their symptoms. Some individuals experience a lot of anxiety by not knowing if they have HD or not and want certainty (100). However, testing remains to be performed voluntarily.

Relevance for PRS in AD

Due to the significant genetic heritability of AD (8), PRS could be used as preliminary screening for people with relatives who have AD. The example of screening for HD is particularly relevant in this context, as both HD and AD are neurodegenerative conditions for which no cure exists at present. Current medical practice focuses on treating the symptoms of the disease to increase the patient's QoL. Even if no cure exists, this test enables individuals to make reproductive decisions and plan for the future (Edge, 2008).

Assessing the risk for AD in patients with relatives with AD may allow these patients to adapt their life course or engage in clinical research. It may furthermore ease the anxiety induced by the uncertainty of the risk. First-degree relatives and adult children of parents with AD show interest in genetic testing and counseling for AD (101). Currently, this screening is not routinely offered to patient relatives in Belgium, mainly because of a lack of treatment modalities (102). However, families in which dementia in general, or AD specifically, is frequently encountered can ask their GP for a referral to a Centre on Human Heritability, where genetic testing for heritable causes of dementia can be performed (103).

Implementation in clinical practice

The implementation of preliminary screening in relatives of AD patients in Belgium requires AD to be added to the list of hereditary diseases for which individuals can inquire about testing in Belgium.

3.3.2. Diagnosis

Currently, the diagnosis of AD in living patients is a clinical and exclusionary diagnosis based on the gradual and continuing decline of cognitive function from a previously higher level. This decline results in social and occupational functional decline, memory impairment, and impairment of at least one other cognitive domain (language, praxis, visual processing, construction, spatial abstraction, or executive functioning). The prerequisite for the diagnosis is that symptoms are not due to any other psychiatric, neurologic, or systemic disease and do not occur exclusively in the setting of delirium (104). The objectivation of cognitive decline is mainly done using a neuro-psychological assessment, after which imaging and/or the evaluation of biomarkers are used to support the diagnosis (The diagnostic process of MCI). However, imaging studies can only confirm a diagnosis of AD in the presence of symptoms, while the benefits of DMTs can be observed in early treatment only (105).

Early symptoms guiding further diagnostic testing have been a proposed strategy in the Chinese population with symptoms that may indicate lung cancer. Research has shown that PRS is an independent risk factor for lung cancer, regardless of age and smoking pack years (106). In this case, the knowledge of PRS status may serve two distinct purposes: first, PRS could guide reimbursement of further diagnostic testing with X-ray

(e.g., from an earlier age onward). Second, as diagnostic testing using X-ray is not without risk – though low-risk, (repetitive) radiation may induce cancer – PRS may support physicians in weighing the risks of diagnostic investigations against the benefits of early treatment in case of symptoms such as coughing, wheezing, and others.

Another example of the value of PRS in diagnostics is the use of PRS profiles in patients experiencing a first psychosis. Psychosis is the result of a complex interplay of genetic risk, brain development, and exposure to stressors or trauma. It can, therefore, manifest as a consequence of mental disorder (schizophrenia, bipolar disorder, severe depression, etc.) (107), a result of substance misuse (108), a symptom of neurological disorders (temporal lobe epilepsy) (109) or be medication-induced (110). It is thus difficult to provide an early diagnosis, yet correct prevention of psychotic episodes is imperative to prevent (further) neurological damage (111). Currently, a PRS has been discovered that is strongly correlated with schizophrenia, a mental/neurological disorder heavily impacting the lives of patients and their relatives. The use of PRS in such cases may lead to early diagnosis of schizophrenia and prompt treatment.

Relevance for PRS in AD

Due to the difficulties in diagnosing AD in living patients, due to the costs of neuroimaging, the invasiveness of CSF-sampling (18,104), and the need for symptom presence (105), PRS could be helpful to support the AD diagnosis, e.g., in patients with subjective cognitive decline (**SCD**). Neurological changes can be observed in these patients, yet disease symptoms are not yet fully present. By combining PRS with other biomarkers, a diagnosis could be made more accurately early in the disease process, allowing timely treatment. Furthermore, PRS can be obtained via a blood or saliva specimen, which makes it less expensive and possibly non-invasive. To support the diagnosis, the use of a phenotype PRS or gene set PRS is most likely.

General PRS:

APOE4 plays an important role in the development of AD (112) yet does not fully capture the genetic heritability of AD (9). As such, in APOE4-negative patients with MCI, the use of PRS may contribute to earlier diagnosis of AD (113) through a PRS in which APOE4 is not included.

Gene set PRS

Furthermore, PRSs presumably associated with age-related cognitive impairment, thus most likely refuting the diagnosis of AD, have been discovered (114). Consequently, the use of PRS for age-related cognitive impairment may significantly reduce the burden MCI places on patients (115), which is at least partially explained by insecurity about future activities and autonomy (115,116). This PRS may especially be relevant in the absence of a PRS indicating high risk for AD (or other significant risk factors) in APOE4-negative patients. In summary, PRS could lead to a more accurate case finding and diagnosis by providing extra genetic information (117).

Implementation in clinical practice

The use of PRS as supportive to the diagnosis should be implemented at a certain point within the diagnostic process, and as such, an optimal point should be decided upon.

3.3.3. Treatment

Treatment of AD currently includes symptomatic therapies such as cholinesterase inhibitors and memantine, and as such, there are limited therapeutic options for AD. Nonetheless, even in the absence of DMTs, PRS can play a role in AD treatment. The current scenarios in which PRS could support treatment in AD are:

1. **The use of PRS to initiate risk reduction strategies:** Knowledge of a high PRS for AD may motivate and stimulate patients to achieve a healthier lifestyle to prevent (further) progression once diagnosed with MCI.
2. **PRS to support personalized medicine:** PRS may support the decision for or against a specific treatment (once DMT is available) based on PRS for efficacy and/or tolerability.

The use of PRS to initiate risk reduction strategies

AD disease prevention should start decades before disease onset, as neurological damage precedes clinical symptoms by decades. Yet also later in life, at the time of MCI and early disease symptoms, lifestyle changes may reduce disease progression and impact of AD on QoL. It is, however, difficult to motivate persons early in life to initiate healthy habits based on risk. A recent umbrella systematic review revealed that even **highly personalized risk information does not strongly affect sustained health-related behavioral changes** (118). As such, more research should be done on how PRS may aid in risk reduction strategies.

Previous studies on returning PRS to patients have produced mixed results. For example, the Genetic Counseling/Lifestyle Change (**GC/LC**) study, which delivered a genetic score constructed from 36 type 2 DM-associated SNPs to overweight patients at risk for DM type 2, reported limited changes in lifestyles and prevention program adherence compared with control participants who did not receive GC (119).

Relevance for PRS in AD

Many modifiable risk factors for AD are well-known: cardiovascular disease, obesity, DM, cancer, etc., all diseases in which subclinical inflammation plays a key role. It may, therefore, not surprise that **non-pharmacological lifestyle interventions addressing AD risk are similar to lifestyle interventions addressing subclinical inflammation** and the diseases mentioned above: exercise, calorie restriction, antioxidant supplementation, nutrition, non-smoking, limiting alcohol intake, and so on (120).

AD is an age-related disease in which risk accumulates over time, similar to cardiovascular disease, DM, obesity, osteoporosis, kidney dysfunction, etc. Common pathophysiological pathways and underlying causes are discovered, such as a dysregulated inflammation pathway (121). Also similar to these diseases is, their presence associated with structural damage: hypertension is the consequence of damaged, less elastic vessel walls; DM of β-cell adaptation (and decompensation) in response to high blood sugar levels. Initiating protective behavior at that point still slows down disease progression. However, displaying "healthy" behavior when the first symptoms of possible AD arise (MCI) might be insufficient due to "damage being done," and further research should evaluate the favorability for further disease progression. Such a strategy may also be applied in patients without MCI (thus earlier in the disease course), though this is unlikely to induce significant behavioral changes (118).

PRS may, combined with a specific screening strategy, allow for preventive pharmacological treatment. For example, by determining PRS in first-degree relatives of AD patients, one could imagine that PRS may stratify between subjects eligible and non-eligible for preventive treatment.

Implementation in clinical practice

To allow for interventions before any symptoms of SCD, MCI, or AD, a screening strategy should be installed to make sure **patients eligible for early intervention are identified**. In patients with symptoms, PRS to initiate risk reduction strategies requires PRS to be obtained in the early stages and, as such, involves no more than adding a blood sample analysis or saliva specimen to the diagnostic procedure.

PRS to support personalized medicine

Gene set PRS:

The efficacy of the medication and the presence of side effects differ individually, based on one's genetics. As such, **gene-set PRS can be used to match patients with the medication best suited for them** (72). This could be cost- and time-saving as treatment choices will be narrowed, and the most effective treatment may be installed earlier than would be the case with random trial-and-error (55). Depending on the options afterward, the implementation of PRS could be cost-effective (106), and treatment choices may be made with more confidence (106).

Phenotype PRS:

In coronary artery disease (**CAD**), the relative risk reduction for CAD with statin use is higher in patients with a high phenotype PRS for the risk of cardiovascular disease (106). It may thus be that **for treatments with a broad effect variability** – such as statins (122) - **PRS can guide treatment decisions**. Furthermore, the cost-effectiveness of statin treatment may improve if considered for reimbursement in high-response profiles based on PRS. Communication with patients with PRS scores for CAD can increase the likelihood of patients with high PRS initiating statins and continuing treatment (even after one year), consequently effectively reducing low-density lipoprotein (**LDL**) levels in these subjects (123).

SNPs:

Furthermore, certain anti-epileptic drugs, such as carbamazepine, are known to cause (rare) life-threatening side effects. In specific individuals, this drug causes agranulocytosis, a condition in which the number of neutrophils is severely decreased, exposing patients to a very high risk for (severe) infection, and aplastic anemia, a life-threatening condition, leaving the patient with a too-limited number of red blood cells to function normally. Currently, PRS have been identified that can identify patients at high risk for these fatal side effects from carbamazepine (106).

Relevance for PRS in AD

Considering the different pathophysiologic pathways in AD, it is most likely that gene set-specific PRS will guide treatment decisions once treatment becomes available (55). Chung et al. (124) **identified gene sets** that have been **associated with specific AD-related neuropathological traits** (neuritic plaques, NFTs, and brain atrophy at particular regions), as well as with typical **cognitive degenerative patterns** and **atrophic brain regions**. Gene set-PRSs have been identified as contributing to the understanding of possibly separable disease processes contributing to disease development in AD and phenotypical heterogeneity in AD (125).

Currently, treatment for AD consists of mainly symptomatic treatment, and PRS is not used to guide decisions herein. However, it may be that certain patients benefit more from treatment than others or are more likely to develop severe side effects, which may affect treatment decisions.

Implementation in clinical practice

The introduction of PRS to guide treatment decisions would require all patients diagnosed with AD (or in whom treatment is considered) to have a blood sample analysis. Depending on the medication and the disease stage it should be provided, PRS will need to be obtained by a different HCP.

3.3.4. Disease progression

Disease progression and the pace with which this happens affect the patient's prognosis and life expectancy and may guide decisions regarding the life planning of both patients and their relatives. Consequently, a PRS that could **differentiate between slow or fast progression** from, e.g., MCI to full-blown AD could support patients and their families in **planning the future life course** but may also **guide treatment decisions** (e.g., weighing of treatment benefits against side effects) based on the prognosis.

While AD displays a considerable phenotypical heterogeneity, which makes disease course prediction early in the disease difficult, for some diseases (e.g., long QT-syndrome), specific variants of modifier genes have been identified that predict clinical severity and thus guide risk stratification and treatment urgency (126). Similarly, the PRS identified for schizophrenia may provide information to psychotic patients on their further life course and impact their life planning (127).

Relevance for PRS in AD

The gene sets identified by Chung et al. (124) associated with specific AD-related neuropathological traits, typical cognitive degenerative patterns, and atrophic brain regions may also be relevant for predicting the patient's disease progression and prognosis. Furthermore, **gene set-PRSs** have been identified as contributing to the understanding of **possibly separable disease processes** contributing to disease development in AD and phenotypical heterogeneity in AD (125). Determination of such PRSs in patients may guide expectations on disease progression, treatment goals, and life planning in general. The gene set-PRSs currently identified in relation to AD risk are the inflammatory response, lipid metabolism, and endocytosis (127). Such strategies are currently not being used in AD diagnosis and treatment plans; their relevance should be further investigated and will depend highly on the availability of new treatments and their mechanisms of action.

Implementation in clinical practice

PRS in prognosis prediction may be easily implemented in clinical practice as it requires a blood sample analysis or saliva specimen. However, there are some ethical implications, as the prognosis may impact treatment options or life choices.

4. Considerations

While valuable contributions are expected from PRS in AD, there are still hurdles hampering solid implementation in drug development and clinical practice.

4.1. PRS methodology

First**, the methods through which a PRS is developed** and calculated imply some considerations. There are several methods to calculate PRSs (128), and as such, different methods may include different SNPs to establish the most accurate PRS based on the methodology used. It is unclear which method is best suited to make accurate predictions (129).

Furthermore, **the sensitivity and specificity** – and thus the predictive value - of PRS is debatable. Combined with the limited genetic heritability of AD (8), it is clear that PRS cannot provide a binary yes/no answer to whether someone will develop AD. Consequently, thresholds should be defined to determine whether or not a patient presents with the label "high risk." This threshold should be based on

- the **absolute risk for disease development** in these "high-risk" patients,
- the **cost-effectiveness** of interventions related to the detection of high-risk,
- the **risk-benefit ratio** of **falsely informing** someone about a high risk.

The latter may lead to the administration of unnecessary (and perhaps harmful or high-risk) treatments or pointless follow-up or diagnostic evaluations.

On top of these uncertainties surrounding PRS, the added value of PRS to predict AD risk is limited, as several studies have demonstrated that AD PRS may not be more predictive than APOE4 alone (130).

At last, PRS suffers from a **portability problem**. That is, a score based on the genetic ancestry in one population does not necessarily hold the same predictive value in other populations: the scores do not "port"

well across populations. As most existing data are from populations with European ancestry, current scores do not hold the same predictive value across other populations (131). Furthermore, these predictability scores do not account for demographic information, which may affect the likelihood of developing a disease, even within subjects from the same ancestry. To date, how scores should be applied **across groups of different ancestries** or within groups of the **same genetic ancestry but with different demographics** is not well established (131). As such, in other populations, identical threshold values would lead to the assignment of "high risk" labels to patients with a different real AD risk.

4.2. Practical implications

4.2.1. Early detection and diagnosis

As PRS is a risk score, there will always be **the need to combine PRS with biomarkers or imaging**, allowing early AD detection. Currently, the available biomarkers are considered invasive (CSF) or expensive (PET). While plasma-biomarkers, which may be obtained less invasively and at a lower price, for the early detection of AD are being researched, currently, there are no accessible tools for the early diagnosis of AD aside from ruling out other causes of MCI (132).

4.2.2. Communicating risk

Aside from the methodological shortcomings, it should be noted that **the concept of "risk" is complex for both patients and physicians** (133). HCPs will need extensive training on genetic liability, the utility of PRS, and patient communication. Simultaneously, efforts should be made to increase the public's genetic literacy and understanding of the risk concept (133). On top of the challenges related to communicating high risks to patients, one should also consider the downfalls of communicating low-risk to patients. There is the **risk of assigning too much value to PRS** and overlooking the impact of other risk factors when considering AD. PRS only subtly improves the ability to predict AD, and the disease will most frequently occur in people without high AD-PRSs. It is thus important not to overemphasize the value of PRS (42). As a consequence, models that predict total AD risk based on the combination of different AD risk factors should be developed, as the use of PRS alone may create a false sense of reassurance in patients in whom no PRS for AD has been identified (42).

4.2.3. Target population

It is unsure in which population AD PRS should be determined. Different scenarios for using PRS in AD screening have been proposed, each raising considerable questions and holding several practical implications.

1. The scenario of **newborn screening** requires informing (future) parents about the PRS, its advantages and disadvantages in a very emotional state (becoming a parent or being a new parent). Therefore, receiving written parental consent or respecting the parent's refusal would be mandatory.
2. Another screening strategy is to offer screening to **patients with significant risk factors for AD**. To date, however, it is unclear **who these patients are**. For example, should PRS screening be offered immediately when a diagnosis of DM, a risk factor for AD, is made, or only a couple of years after that? And what to do with controlled DM, in which blood glucose levels are normalized with medication? Such discussions are relevant as the duration of DM significantly impacts the risk for AD development (134). Similarly, head injuries have a wide variety in severity, and the number of head injuries may influence AD risk (135). Furthermore, screening of patients with significant risk factors would affect numerous patients and HCPs: GPs at most, but also emergency physicians (head injury), geriatricians (old age), and endocrinologists (obesity and DM). As such, introducing such a screening strategy may substantially burden the healthcare system.

3. Screening can also be offered to **individuals with relatives diagnosed with AD**. First-degree relatives of patients with (a high PRS score for) AD may fear the presence of a high AD PRS score themselves, which may induce considerable anxiety (136). HCPs treating AD patients should inform their relatives about the possibility of a PRS test. As such, **guidelines and procedures should be developed** regarding **when and how to communicate high PRS for AD** with relatives and with which relatives. In a monogenic setting, guidelines exist on whether or not and how to inform relatives. The most relevant guideline is that the physician is responsible for discussing the significance of genetic information with family members (131). However, for polygenic settings, resources are lacking (106).

4.2.4. Overdiagnosis and -treatment

Aside from the challenges of screening in each target population, screening holds certain risks: PRS may allow for early identification of high-risk patients and a risk-stratified screening/follow-up program. As with any screening tool, there is a **risk of overdiagnosis** (which can cause considerable anxiety and worry) and **overtreatment** (which can induce significant side effects and costs) in those at high risk for certain diseases (131). Furthermore, **currently, available interventions for reducing the risk** of developing AD in the asymptomatic stage are related to cardiovascular health, sleep quality, healthy lifestyle choices, brain-training exercises, etc., which **do not guarantee the prevention of AD** and are not easily applied by potential patients, not even with the knowledge of having a high genetic risk for certain diseases (118).

4.3. Ethical considerations

4.3.1. Target populations

Screening also comes with some ethical considerations related to the target population. For example, as the disease only manifests in late adulthood, and no cure is available, it is questionable whether it is ethical to allow newborn PRS screening, as **the result of a PRS analysis has consequences for the individual's self-concepts and life plans** (137). Herein, PRS screening for AD differs from neonatal screening for diseases manifesting earlier in life and/or that can be treated or prevented by early intervention. Compared to the current neonatal screening for diseases such as cystic fibrosis (**CF**), the difference with AD lies in the pace with which the disease develops after birth and the impact of early treatment initiation shortly after birth. The neonatal screening for CF has led to a significant increase in life expectancy in CF patients with moderate to severe symptoms because of treatment initiation shortly after birth (138). To date, however, for AD, no such treatment is available. As such, the legal framework on which neonatal screening is based will need to be evaluated to determine the possibility of incorporating AD screening using PRS at this stage.

PRS screening in patients with significant risk factors would mean a model incorporating all known risk factors for AD (and their weighed risk) is developed. However, as with PRS, a threshold value would imply a binary yes/no decision tree to decide whether further evaluation is warranted. At the same time, **AD risk is a continuum, and risk predictions are surrounded by uncertainty**.

When offering screening in relatives of AD patients, the same procedure can be applied as the one for HD; more specifically, one can ask for a referral to one of the eight specialized genetic centers in Belgium, where a test procedure, including multidisciplinary counseling with a.o. a psychologist and neurologist is initiated. The main difference between genetic HD screening and PRS-based AD screening is that PRS screening for AD does not provide 100% certainty and remains a risk prediction, which may increase uncertainty in relatives as much as not offering PRS screening.

4.3.2. Informed consent

Despite the chosen target population, the **assessment of AD PRS will require informed consent**, as PRS entails sensitive information about patients and research participants. Such practice can be challenging,

considering **many patients with (early stage) AD already suffer from (at least) MCI**. While this can be overcome in clinical practice by having a legal representative, the presence of MCI poses significant challenges for participation in drug development research.

4.3.3. Embryo selection

Aside from the target populations described above, screening could also be applied in fertility trajectories, where currently, screening is already obliged to avoid implantation of embryos with "severe hereditary diseases" (139). However, in the direct-to-consumer (**DTC**) market, preimplantation testing of embryos using PRS (for diseases such as DM, cancer, and AD) is already offered under the term "advanced embryo screening." Using the ACCE[3] framework to assess the acceptability (ethical and otherwise) of PRS in such a setting immediately reveals that **PRS-based embryo selection is unlikely ever to be acceptable**. Especially for conditions (predominantly) expressed at old(er) age, the impact of environmental factors on disease pathogenesis is significant. Thus, **PRS pre-birth may hold even lower predictive validity than later in life** (140). Another ethical dilemma imposed by embryo selection based on PRS scores is that some diseases (for which a PRS is known) are more prevalent in one gender compared to another. Thus, indirectly – and on a population level – allowing for the risk reduction **selection of these diseases in embryo selection might lead to the unbalanced selection of one gender over another** (140). The one-child policy in China, or the cultural habit of the dowry in India, has already demonstrated the devastating consequences of gender selection at the population level (141). With the portability between patients of different ancestries, allowing PRS to guide antenatal screening may introduce another layer of inequity in clinical practice.

4.4. Data protection

Another precaution to take when using PRS in drug development or clinical practice is the data sensitivity discussed above. **Genetic information is protected under the General Data Protection Regulation (GDPR)**, especially in clinical practice and drug development research. However, companies such as Cytox© (142) already provide consumer reports in which PRS scores for AD are included. These **reports are provided without guidance from doctors or clinicians who can interpret results or provide correct and comprehensive information on the meaning and implications** of these results (143). While this is problematic, it should be noted that the **genetic information** generated through such testing is **not controlled by the person providing the genetic information**. Privacy policies from DTC companies have statements about how they are allowed to use your data if you buy their products, which often include the sharing or selling of genetic information with other companies.

Such practices may have considerable consequences as they may open the gates to **genetic discrimination**, including using PRS information against patients by making life insurance more expensive or less available (131), denying loans, or even employment to specific PRS profiles (144). As such, regulations on the availability and use of PRS data should be developed.

4.5. Cost impact

At last, the cost impact of implementing PRS in research or clinical practice may be considerable. At present, there are no treatments or strategies that can prevent AD from developing or halt disease progress in an early stage. However, preventive interventions (137) can potentially reduce the risk or delay the onset of AD (137). However, it's important to note that these interventions do not guarantee preventing AD. As such, **PRS use in AD is unlikely to be cost-effective at this point**. Nonetheless, PRS can be valuable in AD research and clinical

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[3] ACCE stands for Analytic validity; Clinical validity; Clinical utility and Ethical, legal and social implications.

practice. The latter is demonstrated in the early value model under the assumption of the availability of DMT (Objectives of the early value model).

Part II: Early value model

Table of contents, Part II: Early value model

1. Objectives of the early value model

The early value model aims to **evaluate the potential impact of PRS implementation as a screening tool in the clinical practice of AD diagnosis**.

Therefore, this section undertakes several analyses to explore the potential of an early value model, addressing the following questions.

| What is the potential **impact of PRS within the diagnostic process of MCI**?
  ↘ The current diagnostic pathway was mapped and compared with the path where PRS was implemented as a screening tool. The impact on costs and identified cases was explored.

| What is the potential long-term **impact of a DMT for AD**?
  ↘ An existing model was leveraged and populated for the Flemish context to assess how a DMT would impact the long-term progression of AD. The impact on costs and quality-adjusted life years (**QALYs**) was evaluated.

| What is the potential long-term **impact of PRS in the diagnostic pathway if a DMT for AD becomes available**?
  ↘ The two models of the two previous sections were linked to each other, and the impact on identified cases, QALYs, and costs was explored.

The early value model serves to understand the possible impact of PRS under different (future and thus uncertain) circumstances and aims to guide future decision-making once DMT becomes available.

2. Methods

2.1. Methods

Exploratory literature research and interviews were conducted to develop the most suitable model to answer each research question. If available, existing models were leveraged and adapted to the context and setting of this analysis. Methods of health-economic modeling were applied to quantify health outcomes (identified cases and QALYs) and costs. Expected benefits and costs were calculated using probabilities, resource use, and costs derived from the literature or governmental sources. Cost estimates for PRS were based on literature (145) and expert discussions.

BOX 2.1. Early health technology assessments (HTAs) or early economic models

Traditionally, a (health-)economic analysis is performed after efficacy and effectiveness studies. Results from these studies are then used as input for the cost-effectiveness analysis (weighing the benefits and costs of an intervention compared to another or no intervention). Early economic models apply the same methods in a much earlier phase of a product cycle. Critical data, e.g., on the treatment/intervention effect, is often lacking, so other sources or assumptions are used to populate the model. Results are usually presented as the "potential" or "likely" cost-effectiveness, as key input parameters of the model are yet to be established.

2.2. Scope

Since no DMTs are currently available for AD, some assumptions were made to specify the scope of this analysis. These assumptions have been made based on the current beliefs in AD research and were validated by Belgian experts (Table 1).

In scope	Out-of-scope (excluded)	Explanation
Key target population for DMT: patients with MCI due to AD		If a DMT would become available, it would target patients early in the disease. Patients with a more advanced form of the disease (mild, moderate, or severe AD) would not benefit from the treatment.
Disease context: AD	Other forms of dementia	The pathophysiology of different types of dementia (and thus the PRS) differs substantially.
Disease subgroup: Late-onset AD	Early-onset AD	Patients with young dementia are not taken into account as this population has a different care pathway with other possible benefits and costs associated with it.
Type of PRS: Genome-wide PRS predicting the phenotypical expression of AD.	Gene set PRS Individual SNPs	For identifying patients based on clinical symptoms in an early step of the diagnostic process, a genome-wide PRS predicting these symptoms to result from AD will be best suited.

Table 1.Key assumptions of the early value model. AD: Alzheimer's disease; MCI: DMT: disease-modifying treatment; Mild cognitive impairment; PRS: Polygenic risk score; SNP: single-nucleotide polymorphism.

PRSs in AD can predict different risks (PRS in AD), e.g., a PRS could predict the phenotypical expression of AD, yet a PRS predicting good drug response could also be discovered. As such, **the place of PRS in the value model could vary**, and consequentially, the impact of PRS on detected cases and costs. Based on literature search and expert opinion, this version of the model now focuses on one particular application of PRS.

3. Results

In the results section, the **mapping of the diagnostic process** and the **absolute and relative impact of PRS as a screening tool** on **identified cases and cost per identified case** are outlined, followed by the **development of a Markov model** exploring the **effect of DMT on QALYs, life years and costs**. Finally, the diagnostic process and the Markov model are combined, exploring the impact of PRS as a screening tool on QALYs, life years, and costs under the assumption of availability of DMTs.

To manage the uncertainty in different inputs, some decisions have been made to determine a base case. These decisions will be explained in the relevant sections.

3.1. Impact of PRS within the diagnostic process

3.1.1. The diagnostic process of MCI

It may be surprising that a diagnostic process for AD is not mapped out, while one exists for MCI due to AD. This is due to the ambiguity in AD. While MCI due to AD is an early disease stage of AD, the term AD is only used in later stages, when other than mild cognitive complaints emerge and affect daily life. Furthermore, **the aim of current research for DMTs focuses on the early stages of the AD disease** process, as it has been elucidated that neurological damage precedes AD with years. As the goal of DMT is to prevent or slow down progression, most gains are to be expected when interfering early in the disease course, thus, at the MCI stage. We therefore mapped the diagnostic process for MCI due to AD, as MCI may also have other causes.

The current diagnostic process: a decision tree

The diagnostic process for MCI due to AD has been mapped, starting with **patients aged 65 or more with cognitive complaints**. A schematic overview is provided in Figure 10. A print screen of the actual decision tree, as modeled in Microsoft Excel®, can be found in Appendix 1.
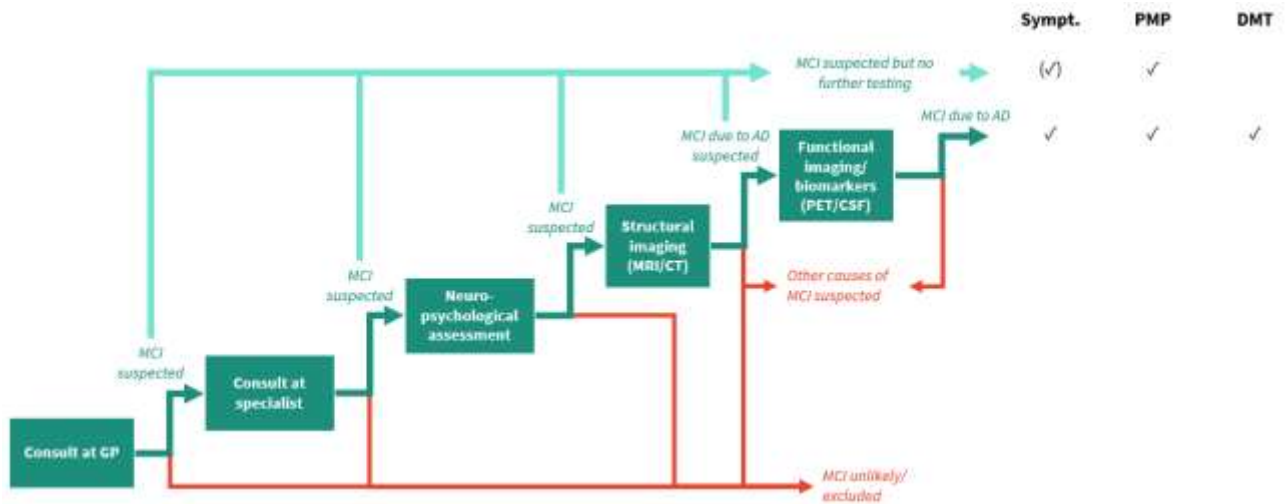

Figure 10. Diagnostic tree for MCI patients due to AD. AD: Alzheimer's disease; CT: Computed tomography; DMT: disease-modifying treatment; GP: general practitioner; MCI: Mild cognitive impairment; MRI: Magnetic resonance imaging; PMP: patient management program; Sympt: symptomatic treatment.

BOX 2.2. A decision tree

A decision tree models a fictitious cohort of people, with different branches representing different pathways depending on choices or probabilities (e.g., the likelihood that a specific event will occur). The cohort moves through the decision tree until the end of a particular path is reached. A decision tree is a relatively simple and intuitive model structure that can be incorporated into a larger model. A disadvantage of decision trees is that they can quickly become quite "bushy"[4] when multiple steps occur sequentially (146,147).

The current **diagnostic pathway consists of five main steps**:

1. clinical examination during a GP consultation;
2. clinical examination during a specialist consultation (e.g., neurologist);
3. neuro-psychological assessment by a psychologist;
4. structural imaging with an MRI scan or CT scan; and
5. functional imaging (PET scan) or a biomarker analysis (CSF analysis).

For each step, the proportion of patients effectively taking this step (e.g., going to the GP, taking an MRI, …) and the proportion of patients per step in whom diagnostic tests warrant further investigation (test sensitivity) needs to be considered.

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[4] Some might even say you can't see the forest through the trees.

An identified case

The model does not require all patients to go through all steps of the diagnostic pathway. It is possible that MCI due to AD is suspected somewhere halfway and that a preliminary diagnosis is made without completing the entire diagnostic pathway. Especially **in the absence of DMT, it is likely that the diagnostic process is interrupted somewhere halfway** as the currently available symptomatic treatment can be provided as soon as a specialist has made the diagnosis and reimbursement criteria are met. For DMT, however, **treatment eligibility likely requires going through the entire diagnostic pathway** until functional imaging.

The impact of PRS

The current diagnostic process, as described above, is compared with a hypothetical (future) situation where AD PRS calculation is applied as a screening tool initiating the diagnostic process. In other words, PRS would come at the beginning of the diagnostic tree and predict the risk of developing AD.

Input parameters

The starting population included in the model are **individuals aged 65+ with cognitive complaints,** as AD usually affects people in their mid-sixties (148). A recent meta-analysis mapping SCD in a 60+ population concluded that approximately one in four older individuals has SCD (149). The 65+ population in Flanders is around 1.4 million (150), so the Flemish population of 65+ individuals with cognitive complaints was estimated to be **357 606**.

An overview of the applied costs and sensitivity/specificity levels of each step in the diagnostic process can be found in Table 2. A detailed description of the input parameters for the diagnostic model is provided in Appendix 2.

		Total cost	Weight	Source	Sensitivity	Specificity	% patients taking this step	Source
PRS		€ 100	100%	RIZIV/INAMI (Jan 2024)	78%	77%	100%	1
GP		€ 30	100%	RIZIV/INAMI (Jan 2024)	66%	74%	Current: 50% PRS: 100%*	2
Specialist	**Neurologist**	€ 61.74	56.86%	RIZIV/INAMI (Jan 2024)	63%	63%	88.52%	3
	Geriatrician	€ 38.08	43.14%	RIZIV/INAMI (Jan 2024)	63%	63%	88.52%	3
	Neuro-psychiatrist	€ 50.94	0.00%	RIZIV/INAMI (Jan 2024)	63%	63%	88.52%	3
Structural imaging	**MRI**	€ 103.69 + €49.10	50%	RIZIV/INAMI (Jan 2024)	71%	89%	100%	4
	CT	€ 102.66 + €49.10	50%	RIZIV/INAMI (Jan 2024)	80%	85%	100%	5
Functional imaging	**PET**	€ 197.29	95%	RIZIV/INAMI (Jan 2024)	86%	92%	10%	6
	CSF	€ 185.21	5%	RIZIV/INAMI (Jan 2024)	87%	84%	10%	7

*Table 2. Overview of the selected costs, weights, and sensitivity/specificity values of the diagnostic steps in MCI. *The proportion of patients considering going to the GP differs between scenarios. In the current diagnostic pathway, this is set at 50%, while in the path preceded by PRS screening, this is set at 100%. [1]Input from the PRISMA consortium; [2] Arnaoutoglou et al., 2018; [3] Mitchell et al., 2009; [4] Staelens et al., 2019; [5] Wollman et al., 2003; [6] Choi et al., 2022; [7] Mufson et al., 2017. CT : Computed tomography ; CSF : Cerebrospinal fluid ; GP : General practitioner ; INAMI : Institut national d'assurance maladie-invalidité ; MRI: Magnetic resonance imaging ; PET: Positron emission tomography ; PRS : Polygenic risk score ; RIZIV: Rijksinstituut voor ziekte- en invaliditeitsverzekering.*

Base case analysis

Some decisions were made to select **a set of input values that serve as the base case**. Each of these inputs can be varied and challenged in a scenario analysis.

For the base case analysis, the following assumptions were made:

| identified cases are defined as patients completing the diagnostic pathway up until the final step;
| in the absence of PRS screening, 50% of all people aged over 65 with cognitive complaints will address these during a GP consultation;
| in the presence of PRS screening, all individuals aged 65+ with cognitive complaints receive PRS screening and all of those with a high PRS for AD consult their GP;
| the a priori chance of having MCI due to AD does not change after PRS screening. As such, the likelihood of detecting a true positive case in the diagnostic process following screening does not change in any of the diagnostic steps;
| the choice to proceed in the diagnostic process does not change based on PRS.

3.1.2. Identified MCI due to AD cases

Starting from the base case, the absolute and relative number of identified cases was calculated, as well as the proportion of patients in each branch of the tree. The latter is based on the proportion of patients proceeding to the next step in the diagnostic pathway and the sensitivity and specificity of tests performed during that step.

The expected absolute number of identified cases in the **current diagnostic pathway** is 544, representing 1.4% of all 65+ patients with cognitive complaints that have MCI due to AD. If **PRS is applied as a screening tool in the diagnostic pathway**, there would be an additional 304 identified cases, bringing the total number to 848 or 2% of all 65+ patients with cognitive complaints that have MCI due to AD (Figure 3.4).

As mentioned earlier, an identified case may be assumed earlier in the diagnostic pathway, e.g., as someone in whom neuropsychological assessment revealed suspicion of MCI due to AD.

Under this assumption, the expected absolute number of identified cases in the **current diagnostic pathway** is 6 230, representing 16% of all 65+ patients with cognitive complaints that have MCI due to AD. If **PRS is applied as a screening tool in the diagnostic pathway**, there would be an additional 3 489 identified cases, bringing the total number to 9 719 or 24% of all 65+ patients with cognitive complaints that have MCI due to AD (Figure 11).

3.1.3. Cost analysis

In the decision tree, each branch was assigned a cost, considering all the medical resources used in this branch (e.g., GP consultation, imaging, etc.) (Table 2). Given the proportion of the cohort per branch, an average expected cost of the diagnostic pathway can be calculated.

Given the base case, the expected cost of the **current diagnostic pathway** of MCI in the context of AD is €40 per individual and € 14.4 million for Flanders (n=357 605) from a healthcare payer perspective. These costs range from €0 per individual who does not seek medical attention to €411 per individual who runs through the entire diagnostic pathway.

When **PRS is applied as a screening tool in the diagnostic pathway**, the expected cost of the diagnostic pathway would increase to €127 per individual and €45.7 million for Flanders from a healthcare payer perspective. The costs range from €0 per individual who does not participate in the PRS screening program

or seek medical attention to €511 per individual who runs through the whole diagnostic pathway (incl. a PRS screening test).

Similarly, as to adapting the definition of identified cases, the model also allows to change, e.g., the proportion of patients proceeding to the next step in the diagnostic pathway.

In the abovementioned calculations, it is assumed that all 65+ patients with cognitive complaints will receive PRS screening and that all those with high PRS for AD will visit their GP to address these complaints. However, **in a real-world setting, a coverage rate of 100% for a screening program is unrealistic**. Considering the proportion of the population reached in other screening initiatives in Flanders (e.g., breast cancer) and DNA screening willingness proportions found in the literature (151), a coverage rate of 75%[5] was explored.

Given a 75% coverage rate, the expected costs of the **diagnostic pathway** with PRS as a screening tool from a healthcare payer perspective would be €67 per individual and €38.3 million for the total cohort. The cost range would not change, yet fewer people with MCI due to AD would be identified correctly, compared to a 100% coverage rate.

Figure 11 visualizes the identified cases and total costs for the base case and a scenario in which identified cases are defined as those in whom clinical examination by a specialist suspects MCI due to AD. These two analyses explore a scenario in which 75% of the population is screened (instead of 100%) with PRS prior to the diagnostic pathway.
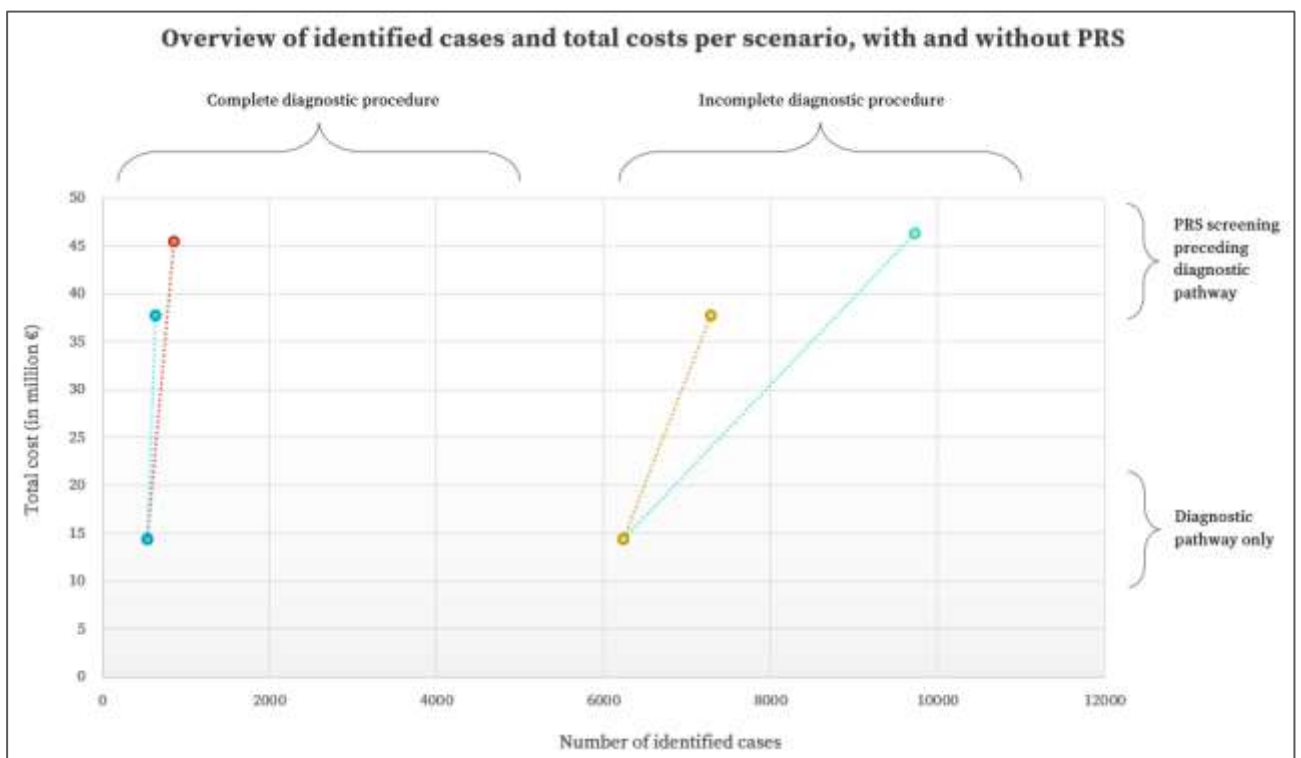

Figure 11. Overview of identified cases and total cost per scenario, with and without PRS. Cost are calculated from a from a healthcare payer perspective. PRS: Polygenic risk score.

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[5] A screening percentage of 75% was assumed based on Belgian breast cancer screening proportions(152) on the one hand, and willingness for DNA screening (151) on the other hand.

3.1.4. Cost per identified case

Assuming these scenarios, calculating the **cost per identified case** provides additional insights into comparing costs with identified cases (Table 3).

	Base case	Incomplete diagnostic pathway	PRS screening 75%	Incomplete diagnostic pathway + PRS screening 75%
No PRS	26 512 €/identified case	2 314 €/identified case	26 512 €/identified case	2 314 €/identified case
PRS	53 604 €/identified case	4 678 €/identified case	29 270 €/identified case	5 172 €/identified case

Table 3. Overview of cost per identified case per scenario. PRS: Polygenic risk score. Cost are calculated from a healthcare payer perspective.

Similarly, incremental costs per identified case can be calculated. An example is provided in Figure 12, assuming the base case.
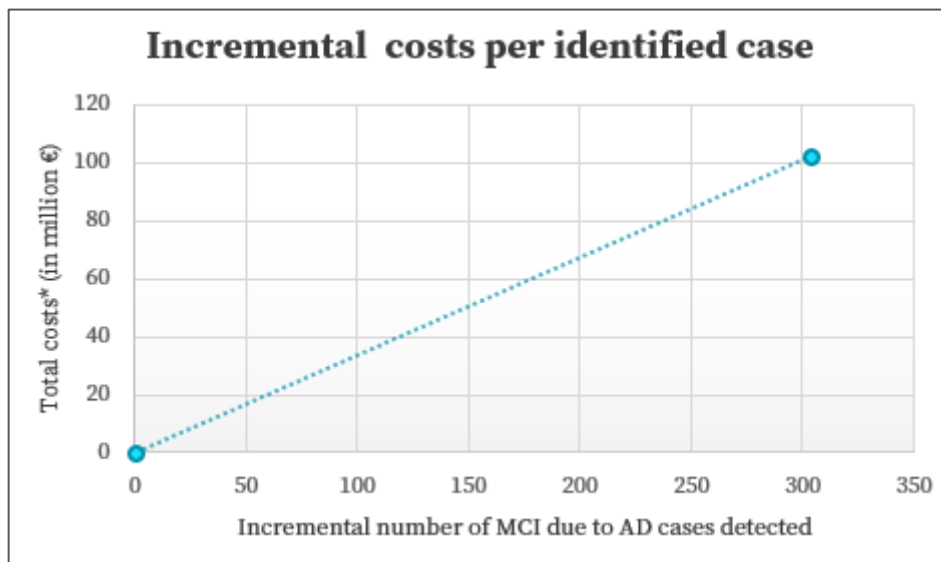

Figure 12. Incremental costs per identified case in the presence of PRS screening before the diagnostic pathway for MCI due to AD, assuming the base case scenario. Costs are calculated from a healthcare payer perspective. PRS: Polygenic risk score.

3.2. Impact of DMT on AD

As DMT for AD aims to slow down or stop disease progression, **AD progression** in itself needs to be **conceptualized**. A Markov model will predict the impact of DMT on QALYs, life years, and costs over a given elapsed time.

BOX 2.3. Quality-adjusted life years

A QALY is an outcome measure expressing the number of life years in a given health/disease state. This health state is described in a value between 0 and 1, with 1 resembling perfect health and 0 equal to death. QALYs are used as outcome measures to compare different (healthcare) interventions (e.g., insulin vs. blood pressure medication) leading to other outcomes (e.g., glycemic control vs. blood pressure reduction, respectively). By expressing both outcomes in QALYs, a direct comparison of intervention effectiveness can be made (146).

3.2.1. Disease progression in AD

The Markov model

An open-source modeling framework is available to **predict disease progression in AD** and **assess long-term health outcomes and cost**s (153). The overall model structure is shown in Figure 13. This Markov model consists of a predementia state (MCI due to AD), 54 AD-states[6], and an absorbing dead-state.
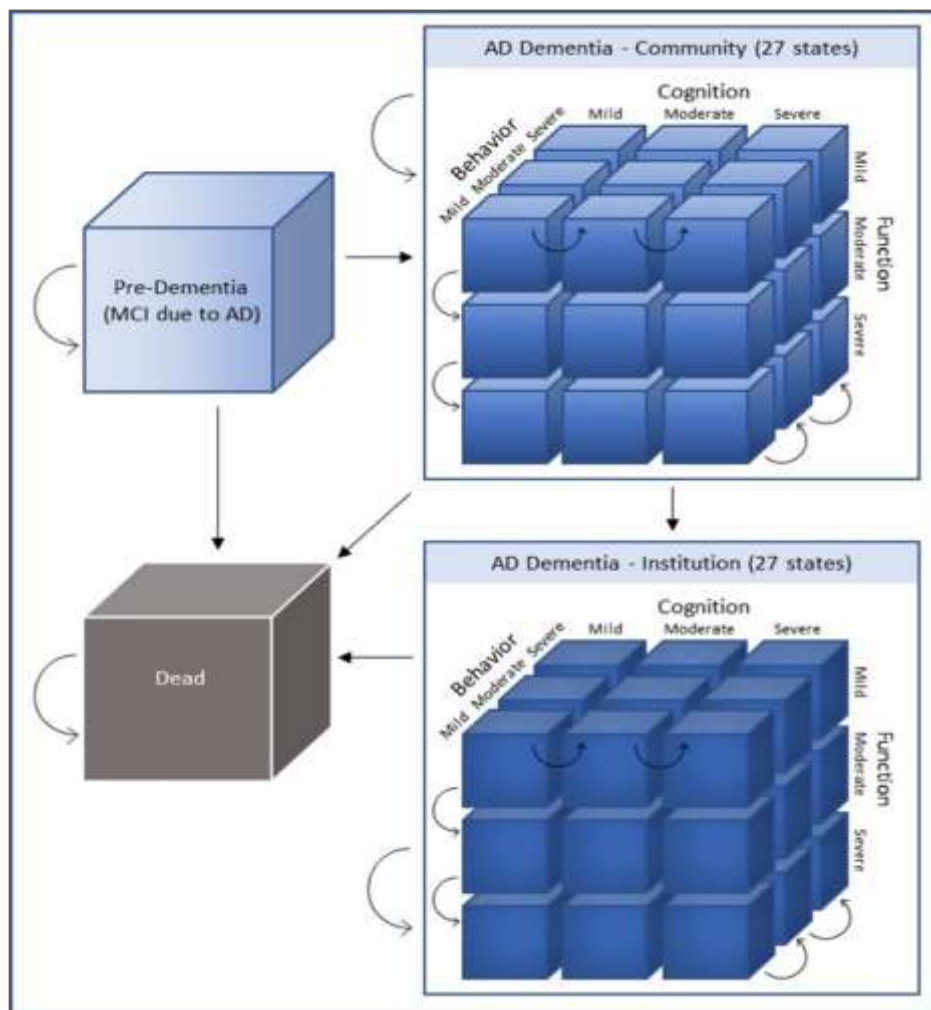

Figure 13. Overview of the Markov Model predicting AD disease progression. Reproduced from Green et al. (2019). AD: Alzheimer's disease; MCI: Mild cognitive impairment.

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[6] Health states for AD dementia are defined based on three symptom domains - cognitive function, behaviour and mood, and functional impairment – each scored on three severity levels - mild, moderate, severe - resulting in 27 (3x3x3) possible AD health states. Next to these 27 possible states, a distinction is made between people with AD living in a community setting vs. in an institutional setting. In other words, all possible AD health states are duplicated, resulting in a total of 54 AD states.

BOX 2.4. A Markov model

A Markov model is a commonly used analytical framework in health economics and uses disease states to represent all possible consequences of an intervention of interest. These disease states are mutually exclusive and exhaustive, and as such, each individual represented in the model can be in one and only one of these disease states at any given time (146).

The starting population of the Markov model is **65+ individuals with MCI**. Note that **the endpoint of the diagnostic tree**, i.e., the diagnosis of MCI in 65+ patients with cognitive complaints, **is the starting point of the Markov model**. The Markov model can be used with and without linking it to the decision tree.

In the first step, by considering the Markov model by itself, a comparison can be made between a world in which DMT is available vs. a world where DMT is not available (assuming all patients with MCI due to AD are correctly identified in both groups).

The impact of DMT

The current AD progression, as described above, is compared with a hypothetical (future) situation where DMT is provided to MCI patients (effectively diagnosed) over a period of time, resulting in slower disease progression.

Input parameters

The model allows to evaluate the number of patients in a specific disease state over a given period, which is impacted by how fast people transition to worse disease states (i.e. disease progression) and to what extent a DMT can slow down this progression. Each state has a value regarding QALYs, expected mortality this state brings to someone, and a (direct medical) cost related to the care needed for a person with a specific condition in the given health state (during one cycle).

Transition probabilities, or values indicating disease progression over time, from the original open-source model were used (153), as no Belgium-specific data were available (except for mortality risk). In this model, patients can remain in the same health state (regardless of the state), progress from MCI to AD, progress through the different AD stages, go from a community to an institutional setting, or die.

The estimated mortality risk in AD was calculated based on the increasing relative risks (Table 4) and age-specific mortality rates of the Belgian general population (154). Due to a lack of data, no differentiation between community and institutional settings was made.

Disease stage	Relative risk	Source
MCI	1	(155)
Mild AD	2.92	
Moderate AD	3.85	
Severe AD	9.52	

Table 4. Mortality risk: relative risk according to AD severity. AD: Alzheimer's disease; MCI: Mild cognitive impairment.

Costs related to the different AD states were derived from a Belgian cost analysis and can be consulted in Table 5 (156). These costs relate to the care patients in these health states need without DMT costs.

	Healthcare payer perspective	Source
Community setting		
MCI	€ 4 598	1
Mild AD	€ 6 939	2
Moderate AD	€ 20 422	2
Severe AD	€ 22 482	2
Institutional setting		
Mild/moderate/severe AD	€ 51 099	3

Table 5. Annual cost of AD, according to disease severity. 1: OECD; 2: Vandepitte et al., 2020, 3: Kostprijscalculatie Zorg24. AD: Alzheimer's disease; MCI: Mild cognitive impairment.

Costs for DMT were based on literature (157) and expert opinion, as no DMT for AD is currently available. Similarly, the effectiveness of DMT on disease progression is based on literature (156) and expert opinion due to the lack of available data.

Utilities were derived from a recent meta-analysis (158). These are proxy-derived values (i.e., the caregiver filled out the questionnaire instead of the patient) based on the EQ-5D. Although the setting in which a patient resides likely impacts utility values, Landeiro (2020) (158) argues that current evidence is insufficient to adapt these utilities based on the setting. Hence, it was conservatively assumed that utilities do not differ between the community and institutional setting (Table 6).

	Community setting	Institutional setting	Source
MCI	0.80	/	
Mild AD	0.74	0.74	(158)
Moderate AD	0.59	0.59	
Severe AD	0.36	0.36	

Table 6. Utilities for MCI, mild, moderate, and severe AD in community and institutional settings. AD: Alzheimer's disease; MCI: Mild cognitive impairment.

Base case analysis

Some decisions were made to select **a set of input values that serve as the base case**. Each of these inputs can be varied and challenged in a scenario analysis.

For the base case analysis, the following assumptions were made:

| DMT reduces treatment progression by 30%;
| DMT can effectively reduce disease progression for 5 years, after which treatment is stopped without prolonged effects, leading to a return of normal disease progression afterward;
| 10% of patients discontinue treatment each year;
| the annual treatment cost is €10 000;
| all patients start in the MCI health state;
| a time horizon of 20 years is applied, with a cycle length of one year;
| cost are discounted at 3%, whilst QALYs at 1.5%

3.2.2. QALYs, life years and costs

Starting from the inputs determined for the base case, the **absolute costs, life years, and QALYs per person** were calculated in both the absence and presence of DMT.

In the **current situation**, where no DMT is available, the healthcare costs per person over a 20-year horizon are estimated at € 131 866. Without a DMT, a person with MCI is expected to have a life expectancy of 11.24 years or – if adjusted for the expected QoL – 7.83 QALYs.

When **DMT is available**, the cost per person over a 20-year time horizon would rise to € 150 472. The expected life expectancy of a patient would be 11.61 years or 8.26 QALYs.

As mentioned earlier, the **effectiveness of DMT is currently an assumption** based on literature research and expert opinion and may thus be higher or lower. For example, assuming a reduction in disease progression of 45% (instead of 30%), costs per person over a 20-year horizon would decrease to €147 269. At the same time, health outcomes would increase to 11.82 years or 8.49 QALYs per person. Costs, life years, and QALYs per person in the current situation (without DMT) would remain the same as there is no DMT.

3.2.3. Incremental cost-effectiveness

Assuming the base case, **the incremental cost-effectiveness ratio (ICER) can be calculated** by comparing a situation with a situation without DMT.

> **BOX 2.5. Incremental cost-effectiveness ratio**
>
> An ICER allows weighing the additional cost of an intervention compared to another intervention by dividing these additional costs by the additional gains of that intervention compared to the gains of that second intervention, with the gains typically expressed as QALYs. The ICER thus allows the comparison of different, non-related interventions and can guide optimal budget spending by calculating which intervention will provide the most additional value for money.
>
> $$ICER = \frac{COST\,intervention\,B - COST\,intervention\,A}{QALY\,intervention\,B - QALY\,intervention\,A}$$

In this scenario, the number of QALYs gained is 0.424, while the additional cost is € 18 606. As such, the ICER of a DMT able to reduce disease progression by 30% for 5 years (compared to no DMT) results in an ICER of € 43 868/QALY gained. Figure 14 visualizes both the absolute and incremental cost-effectiveness planes.
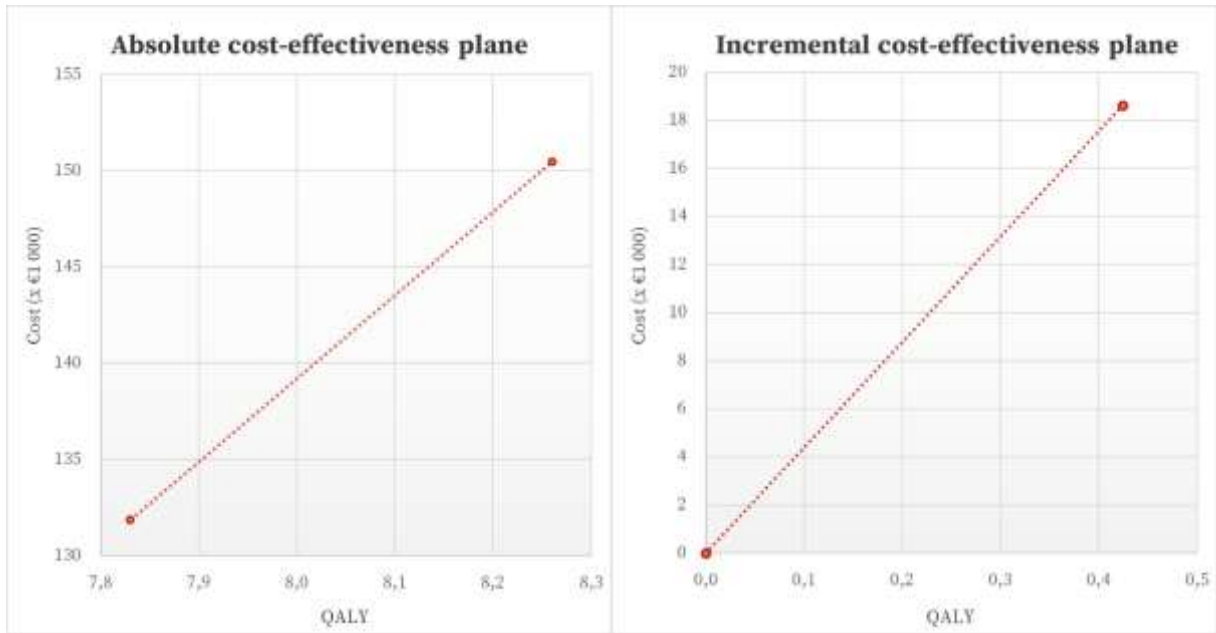
Figure 14. Absolute and incremental cost-effectiveness planes representing the base case with and without DMT. Costs are calculated from a healthcare payer perspective. DMT: Disease-modifying treatment; QALY: Quality-adjusted life-year.

3.3. Impact of PRS on AD management (diagnosis and treatment)

As a last step of this value model, the two previous models are linked together. The decision model captures the diagnostic pathway, while the Markov model incorporates the long-term progression of AD. This enables the assessment of the potential **long-term benefits and costs of PRS in the diagnostic pathway in case a DMT for AD becomes available**.

From our decision tree, we know there are 4 subgroups:

| those with MCI due to AD and correctly identified as such;
| those with MCI due to AD but not identified;
| those without MCI due to AD and correctly identified as such;
| those without MCI due to AD incorrectly identified as having MCI due to AD.

The decision tree was developed in two versions, one in which PRS is incorporated in the diagnostic pathway as a screening tool and one where it does not (i.e., current diagnostic pathway). Hence, 8 endpoints are possible in the decision tree.

For each population, a separate version of the Markov model is linked to each endpoint of the diagnostic tree. In other words, **the distribution resulting from the diagnostic decision tree was used as input for the Markov model**. This differs from the situation in which the Markov model was used to assess the impact of DMT alone, without incorporating the diagnostic tree (3.2, Impact of DMT on AD).

From this model, we know that disease progression and, thus, health outcomes (QALYs and expected life years) and costs differ in a scenario where DMT is (not) available. Hence, when combining both, each of the diagnostic tree's endpoints is linked with the scenarios of DMT availability and unavailability. As such, sixteen scenarios are possible.

To evaluate the impact of PRS on AD management, the scenarios in which no DMT is available are not considered. In other words, to assess the impact of PRS on AD management, **the two following situations are compared (Figure 15)**:

1. the total cohort of patients aged 65+ with cognitive complaints entering the diagnostic pathway, in which the subgroups resulting from the diagnostic pathway enter the Markov model, in which DMT is assumed,

versus

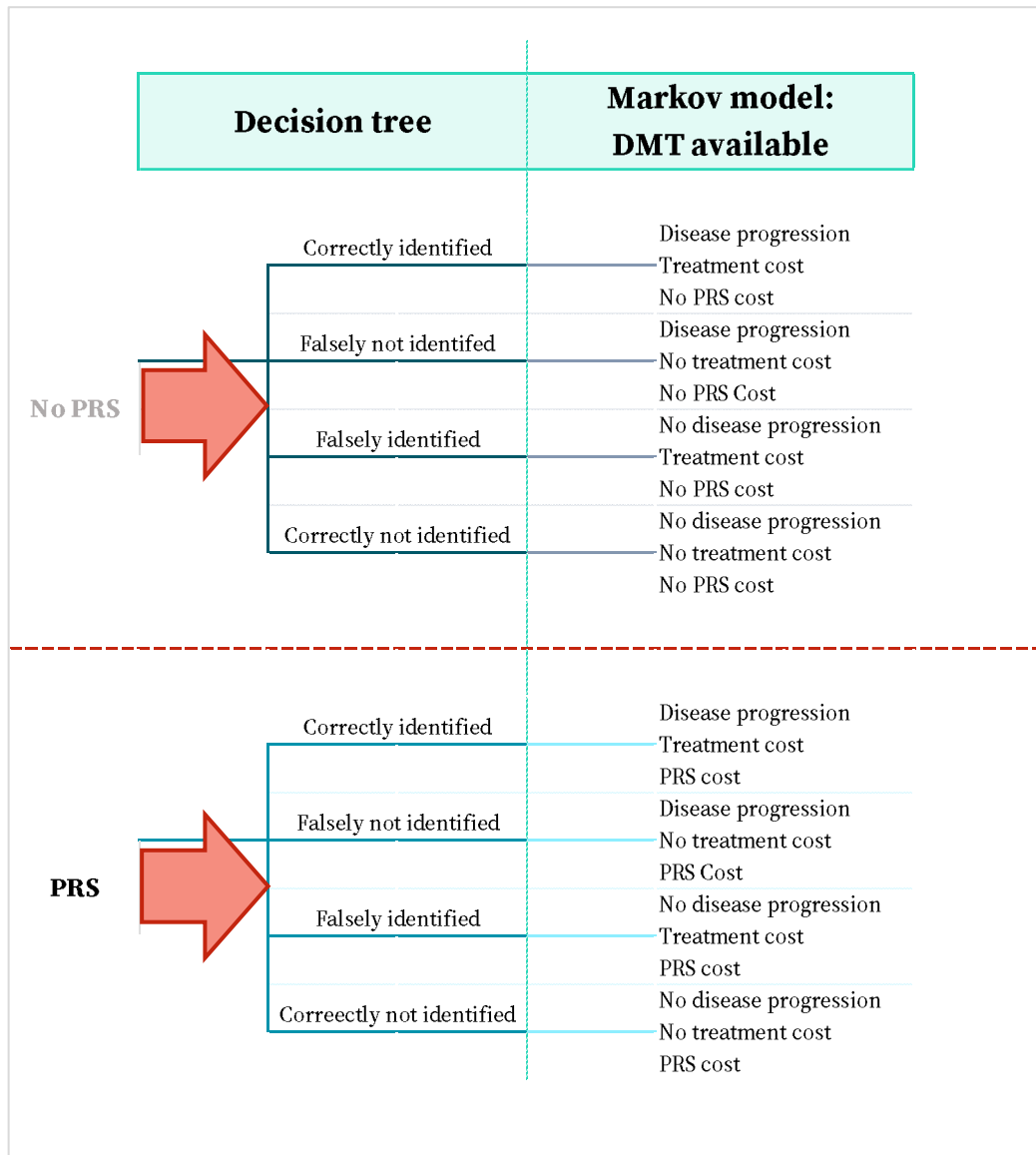2. the total cohort of patients aged 65+ with cognitive complaints having access to PRS screening, followed by the diagnostic pathway. Again, the subgroups resulting from the diagnostic pathway enter the Markov model, in which DMT is assumed.

Figure 15. Linking the decision trees (with and without PRS) with the Markov model. DMT: Disease-modifying treatment; PRS: Polygenic risk score.

Assuming the base case of both the decision tree (The diagnostic process of MCI) and the Markov model (QALYs, life years and costs), for each outcome arm (or subgroup), the QALYs, life years and costs can be calculated (Table 7).

Subgroup	Number of patients, cost, QALYs, and life years				
	Correctly identified MCI patients	Falsely not identified MCI patients	Falsely identified MCI patients	Correctly not identified MCI patients	Total population (65+ with cognitive complaints)
No PRS/PRS	544/848	39 508/39 204	2/1	317 552/317 552	375 606
Cost	€ 150 472	€131 868	€ 93 374	€ 59 822	€ 67 919
QALYs	8.26	7.83	11.69	11.69	11.26
Life years	11.61	11.24	14.62	14.62	14.24

Table 7. Overview of the number of patients per subgroup, costs, QALYs, and life years assuming the base case for the decision tree and the Markov model. The total population refers to the total population of 65+ aged patients with cognitive complaints in Flanders. Costs are calculated from a healthcare payer perspective. MCI: Mild cognitive impairment; PRS: Polygenic risk score; QALY: Quality-adjusted life-years.

Weighing the costs and QALYs per subgroup, the total number of incremental costs and QALYs per person can be calculated (respectively € 103 and 0.0004), from which the ICER of PRS screening preceding the diagnostic process of AD compared to no PRS can derived. This results in an ICER of €284 061/QALY gained.

BOX 2.6. Willingness-to-pay (WTP) threshold

The WTP threshold refers to **the maximum amount a decision-maker is willing to pay for a unit of health outcome** (e.g., 1 extra QALY, or in other words, one additional year in perfect health). There is no universal, fixed WTP threshold. The United Kingdom (**UK**) handles a fixed, country-specific threshold of 30 000 £/QALY, while the threshold is variable for Belgium. A commonly used value is 40 000 €/QALY gained, derived from the cost of dialysis, and that also aligns with the gross domestic product (**GDP**) per capita for Belgium. In 2015, the Dutch Healthcare Institute (Zorginstituut Nederland, **ZIN**) proposed differential thresholds depending on the disease burden. A WTP threshold of 80 000 €/QALY is accepted for a high disease burden. This approach has also found its way in Belgium, for example, at the RIZIV/INAMI[7].

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[7] RIZIV: Rijksinstituut voor ziekte- en invaliditeitsverzekering; INAMI: Institut national d'assurance maladie-invalidité.

Figure 16. Incremental cost-effectiveness plane, showing different willingness-to-pay thresholds and the base case ICER of PRS with a DMT vs. no PRS. Costs are calculated from a healthcare payer perspective. ICER: Incremental cost-effectiveness ratio; QALY: Quality-adjusted life-years; WTP: Willingness-to-pay.

Considering the WTP threshold, it is unlikely that PRS, as a screening tool preceding the AD diagnostic pathway, would be regarded as a reasonable investment under these base case inputs and assumptions (Figure 16).

As the decision tree and the Markov model are linked together, these **results are impacted by input parameters in both of these models**. For example, suppose an effective DMT becomes available and functional imaging is required to determine eligibility for this treatment. In that case, it is unlikely that the probability of undergoing functional imaging (PET or CSF) would remain as low as 10% (i.e., base case input). If this would increase to 90%, the ICER would reduce to € 70 796/QALY gained.

4. Discussion and considerations

In this value model, we have developed both a decision tree and a Markov model, simulating respectively the diagnostic process of AD in Flanders and the disease progression of AD, including costs, QALYs, and expected life years, adapted to the current situation in Flanders. By incorporating PRS screening in the diagnostic tree (preceding the current diagnostic process) and the availability of DMT in the Markov model (affecting transition probabilities and costs), the **early value model allows to evaluate**:

- the **impact of PRS** within the diagnostic process on the **number of correctly identified MCI due to AD cases**, the **costs** implicated with this process, and the **incremental cost per identified case** (3.1, Impact of PRS within the diagnostic process);
- the **impact of DMT on disease progression, QALYs, life years, costs**, and the **incremental cost-effectiveness** of DMT (Impact of DMT on AD);
- the **long-term impact of PRS** preceding the diagnostic pathway on AD, assuming the availability of DMT.

Implementing PRS in (AD) **screening requires evidence of a benefit to society to justify allocating resources** to it. Based on the last step of this value model, combining the decision tree with the Markov model, it can be stated that the added value of PRS screening in the population aged a minimum of 65 years with cognitive complaints would be limited under the base case assumptions. The model has shown that assuming the base case, the impact of PRS as a **screening tool positively affects the proportion of identified cases**. However, the ICER shows high incremental costs per QALY gained when looking at the potential long-term impact.

This finding should be seen in light of the **limited robustness of the results**. Exemplary is how the number of identified cases impacts the ICER. Assuming the base case, PRS + diagnostic pathway identifies 304 additional cases (or 848 in total). While this is a 56% increase compared to no PRS preceding the diagnostic pathway, the **number of identified cases remains limited** to about 2% of the 65+ population with cognitive complaints. As such, the clinical value may be debatable, and the ICER (€ 284 061/QALY gained) does not support the investment from a healthcare payer perspective. However, the base case assumes that identified cases have completed the diagnostic pathway until the end. Based on the current diagnostic pathway of MCI, the last step of the diagnostic process (the proportion of patients undergoing a PET scan or CSF evaluation) would only be taken by 10% of the patients remaining in the cohort at that point. However, if this step were required for eligibility for DMT, it is most likely that more (not to say almost all) patients would take this step. Assuming a 90% transition instead of 10% would lead to 7634 identified cases (2740 additional identified cases compared to no PRS (n = 4893)). Consequently, 19% of all MCIs due to AD cases instead of 12% would be identified. Again, an increase of 58%, yet the **clinical relevance of PRS increases dramatically due to the more significant absolute effect**. On top of this, as more patients are identified and thus treated, the ICER would drop to € 70 796/QALY gained, which does fall below a WTP threshold of 80 000€/QALY (Figure 16). Similarly, reducing the price of PRS from €100 per test to €50 – without adapting other costs – reduces the ICER to €145 608, almost half of the ICER under base case assumptions.

These are just two examples of the model's adaptability, allowing the alignment of **transition probabilities or costs with a future reality or assumptions**. This also shows that by changing only 1 parameter, the result and conclusions of the value model can drastically change. **Considerable variability in results** and a lack of robustness is a recognized issue in cost-effectiveness studies of preventive interventions. This is because health gains and incremental costs are minimal individually, resulting in an **unstable ratio** (i.e., the ICER). This is particularly challenging in early value models, where many inputs rely on assumptions.

Another uncertainty in this early value model is the **test sensitivity and specificity of PRS**. Test characteristics were based on results from the Kunkle GWAS study (40). Yet, there are several methods to calculate PRSs (128). As such, different methods may include different SNPs, resulting in a PRS with different predictive values, sensitivity, and specificity (PRS methodology). A recent (ongoing) study evaluated a new PRS for AD, in which sensitivity and specificity were 62% and 82%, respectively. Using these values instead of those in the base case (78% and 77%, respectively), the ICER rises through the roof to € 567 051/QALY gained. Again, this significant deviation from the base case results from the unstable ratio. On the other hand, it might be assumed that, with time passing, **research in PRS will evolve, and more accurate, sensitive PRSs will arise**. Given the high variability in ICER, this may also lead to a reduction in ICER. Indeed, when sensitivity and specificity increased by approximately 10% (from the base case) to 85%, the ICER dropped to € 226 871/QALY. Still, this number is far from typical WTP thresholds (€ 40 000 to € 80 000/QALY gained).

This demonstrates the **impact of the diagnostic process** – the decision tree – preceding treatment. Under base case conditions, thus identifying approximately 2% of all AD patients, achieving an acceptable ICER is impossible. It is, therefore, interesting to explore the **possibilities of adapting the diagnostic process**, for example, by using PRS to support a diagnosis of AD rather than as a screening method. In such a scenario,

PRS might replace CSF or PET examination at the end of the diagnostic process. Assuming a realistic 75% of patients proceeding with PRS after going through the previous diagnostic process steps, the number of identified cases would increase to 3 696 compared to 848 in the PRS arm. In this scenario, where more cases are identified, and costs for performing CSF evaluation or MRI can be left out, the ICER would become dominant[8], assuming base case conditions. This is one example, yet PRS assessment could be placed anywhere within the diagnostic tree as an additional step or as a replacement for (an) another step (s). This example demonstrates that the early value model can be adapted accordingly depending on the evolution of AD research and practice.

Similarly, the early value model allows the building of additional steps or adapted pathways for specific patient groups. For example, it might be overly optimistic to assume that all individuals aged 65+ with cognitive complaints would want to be screened. In the cost analysis of 3.1.3, only 75% of patients receive PRS screening. It would, however, not be correct to assume that those not eager for PRS screening would not undertake any action at all. Therefore, the value model allows **redirecting those patients to the "no PRS-arm,"** in which they follow the diagnostic process proportionally and add to a limited number of identified cases (n = 80 in case of a 75% PRS screening rate). Again, this is another example of how the value model allows adding (or removing) steps within the process to **refine its alignment with reality** or assumed circumstances.

Moreover, the early value model can be used to **simulate situations to guide decisions, such as modeling the optimal diagnostic process or assessing the maximum annual treatment price for cost-effectiveness based on the** disease progression reduction of DMT. Figure 17 visualizes the annual DMT costs and effectiveness (disease progression reduction) required to remain under the threshold of €30 000, €40 000, or € 50 000 per QALY gained, respectively (without linking the Markov model to the decision tree). While, in this case, the annual DMT cost varies over a given ICER and DMT effectiveness, the model allows the specifying of a value for any of the output parameters and calculating the value for a given input parameter under constant circumstances for the other parameters.

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[8] When an intervention demonstrates both clinical benefits and cost savings (vs. its comparator), it is referred to as a "dominant" strategy.
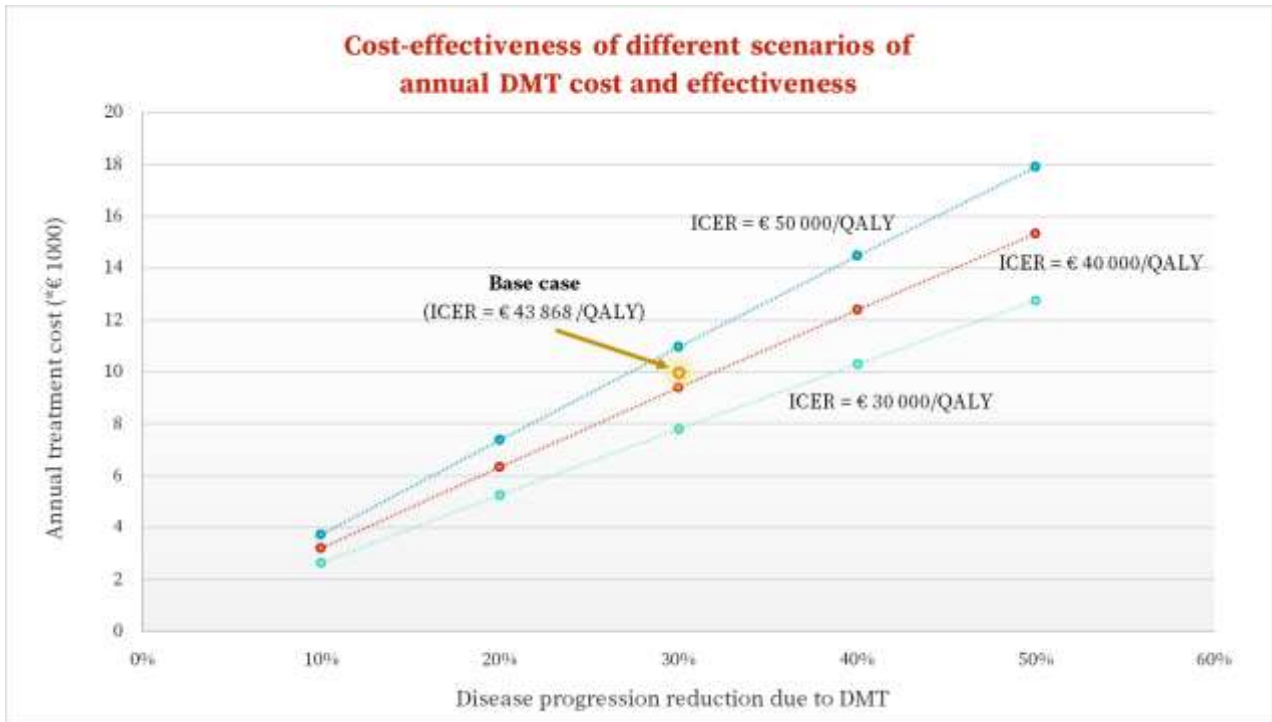
Figure 17. Cost-effectiveness of different scenarios of annual DMT cost and effectiveness. DMT: Disease-modifying treatment; ICER: Incremental cost-effectiveness ratio.

While the previous examples provide insight into the adaptability of the value model, it should be noted that it also shows that the **different PRSs can be used within the value model** (PRS in AD). For example, a PRS predicting susceptibility to a certain DMT may be included to separate patients benefitting from treatment from those seeing their condition progress without delay. By adapting the transition probabilities per subpopulation accordingly, the early value model may guide, for example, reimbursement criteria.

4.1. Strengths and limitations

It may be clear that an early value model can be a valuable tool to guide and evaluate decisions concerning the value of PRSs. However, some considerations should be made.

As with any model, this is a simplification of reality. Some limitations of this model structure should be taken into account. First, mapping the diagnostic tree of MCI due to AD is challenging, as a definitive diagnosis of MCI or even AD is often not made as a DMT does not exist. Specifically for MCI, this diagnosis is only rarely made as mild memory problems are frequently not discussed early on with an HCP, and various definitions of MCI are used in clinical practice. Consequently, the available information in the literature on the diagnostic process of MCI is limited. Therefore, some steps of this diagnostic pathway are based on diagnostics in AD and/or dementia. Second, we would expect the diagnostic process to be more circular than linear, where results of different tests and consultations are brought together as pieces of a puzzle. Third, the model does not consider repeated testing (e.g., follow-up over time). However, this representation should be seen as a snapshot in time, given the current Flemish 65+ population with cognitive complaints, allowing us to make cost calculations and estimate the potential impact of PRS when included in this diagnostic process.

Another limitation of the early value model is its scope. The value model considers the healthcare payer perspective, yet the societal perspective is not included. Although productivity losses are most likely not very important for the population considered, most of them being retired, productivity losses in informal caregivers of AD patients are known to be high. Fakeye et al. (159) report an on-average productivity loss of

one-third, primarily due to reduced performance while at work (i.e., presenteeism). Vandepitte et al. (156) reported the annual cost for a community-dwelling person from the societal perspective to be almost 2.5 times higher than from a healthcare payer perspective, emphasizing the magnitude of indirect non-medical costs. In future research, expanding the current analyses to incorporate the societal perspective would be interesting.

Conclusion

PRSs have gained more attention over the last decades in research and clinical practice and have even shown their usefulness in clinical practice for some diseases. However, the value and usefulness in AD is still under debate. AD is a heterogeneous, multifactorial disorder, and biological changes occur in the brain already long before the first clinical symptoms emerge. The development of drugs for AD has shown to be highly challenging as no new drugs have been approved over the last 20 years. Current research focuses on developing DMTs, acting earlier in the disease process (i.e., in the prodromal stage, before the first symptoms appear), which makes it challenging to recruit suitable and sufficient participants due to its late diagnosis.

This preliminary landscape analysis, in combination with the development of an early value model, has explored the value and potential of usefulness in AD. The added value of PRS to predict AD risk is limited as AD PRS might not be more predictive than APOE4 alone, which is the strongest genetic risk factor for late-onset DNA. Additionally, it is unclear which method for PRS calculation is best suited to make accurate predictions. The sensitivity and specificity of AD PRS are debatable, and even though it might provide relevant information on the population level, it cannot provide a binary yes/no answer to whether someone will develop AD.

One of the significant limitations of PRS is that it only accounts for genetic information, resulting in a static risk score. PRSs do not consider environmental and lifestyle factors, which may also influence the risk of developing a disease, nor the dynamic nature of the disease, which progresses over time. To encounter the more static character of PRS, PRS could be used in combination with more dynamic measures such as biomarkers, transcriptomic data, and epigenetic data.

One of the areas where PRS could bring added value, especially when combined with dynamic measures, is the identification of AD patients in the early stages of AD. As biological changes occur long before the first symptoms in AD, researchers hope to find DMT that can intervene in the prodromal stage of AD. Therefore, it will be essential to identify patients in the prodromal phase with a high risk of developing AD (i.e., not all patients with a high risk of AD develop AD). Combining genetic susceptibility with these dynamic measures could provide insights into the factors influencing AD development and could increase the accuracy of predicting whether the patient will develop AD.

Another area where PRS, combined with the dynamic measure, can bring significant added value is better understanding the pathophysiological mechanisms and identifying potential new targets. Especially linking dynamic measures with gene set-specific PRSs or SNPs related to AD might provide new insights for further research. For example, linking transcriptionally active regions with the SNPs located in these regions can provide more information on the function of these SNPs (i.e., the majority of the SNPs are not near genes with disease-specific functions). These gene set-specific PRSs might also help unravel AD's heterogeneous nature by defining specific AD subtypes in which specific regions are differently expressed. These insights might lead to the development of DMTs specifically targeting the regions/pathways involved in this AD subtype.

If a DMT is available, PRS could also be used in clinical practice, again mainly in combination with a dynamic measure. PRS could aid in identifying patients in the early stages of the disease or help with treatment decisions and prognostic values. For example, a patient's genetic profile can impact the responsiveness or toxicity to a specific treatment. The value model we developed examined the potential effect of using PRS as

a screening tool (i.e., for diagnosing patients in the early stages of AD). The model showed that a PRS used as a screening tool could indeed increase the number of identified cases of MCI. However, the added value does not justify the extra costs when assuming a DMT is available. This finding heavily relies on input derived from the world as we know it, which is likely to change as soon as a DMT becomes available. This also implies that when a DMT becomes available, PRS is only helpful if the diagnostic pathway of MCI improves.

As long as no DMT is available, PRS will only have limited use in clinical practice. However, the actual merit of the value model lies in its adaptability, creating the possibility to evolve together with further research in PRS. Depending on the sensitivity and specificity of AD PRs that can be reached, it will be essential to define the optimal threshold. The value model can help to estimate the impact of the PRs threshold decision on identified cases and the associated costs.

To conclude, PRS, on its own, will be limited in its usability due to its static nature. However, combining PRS with more dynamic measures, such as biomarkers, transcriptomics, or epigenomics, might bring extra insights into the pathophysiological mechanisms of AD and support the identification of valuable DMTs. Combining the genetic footprint of a patient with environmental and lifestyle factors can bring us one step closer to precision medicine for AD.

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Appendices

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5. Appendix 1 – diagnostic pathway with and without PRS screening

6. Appendix 2 – input parameters of the diagnostic pathway

6.1. Estimated percentage of MCI in 65+ population

The first distinction in the diagnostic tree is between the people who do have MCI and those who appear not to have MCI. Therefore, the average percentage of MCI in the elderly was searched for in the literature. According to a meta-analysis study published in 2023, the pooled prevalence of MCI in 376.039 older adults (between 65 and 87 years old) in nursing homes from 17 countries is estimated at around **20%** (160). It has to be noted that this estimation is from older adults in nursing homes and may not project to a realistic 65+ population. According to an American study, **56%** of MCI patients are due to AD (161).

6.2. Step 1: clinical examination at the GP

Belgian experts indicated that, in general, patients with cognitive complaints will consult their GP first. Based on desk research (162) and expert opinion, the assumption is that, on average, a clinical examination at the GP consists of 2 consultations (additional to regular healthcare use). One important aspect of the consultation is the anamnesis, in which the GP asks the patient and/or relative questions about the history and context of the complaints. The GP also often asks questions about risk factors such as age, presence of arterial hypertension, DM, and relevant family history (163).

Technical investigations such as blood analysis, urinalysis, and a cognitive test are performed next to the anamnesis. Input for these parameters was retrieved from De Lepeleire et al. (163). Blood analysis and urinalysis are included in the clinical examination sometimes, often, or always, 93.59% and 73.71% of the time, respectively.

- The mini-mental state examination test (MMSE) is used often to always by 82.78% of GPs and sometimes by 13.6% of GPs (163). Despite growing arguments that other cognitive tests, such as the MoCA, are better at diagnosing MCI, the MMSE is an obligatory test in the reimbursement procedure of cognitive-enhancing drugs (163). Therefore, the sensitivity/specificity values of the MMSE test in GP settings are used (66.4% and 73.5%, respectively) (164).
- According to this study, a minority of GPs also requested imaging. However, as we consider imaging as a separate step in the diagnostic tree, we do not consider imaging in this first step.

Regarding the costs, the nomenclature codes of the relevant services were searched and used in the Nomensoft database. The ambulant option was used for all codes, assuming that the diagnostic process is completely ambulant. A consult at a GP is €30 (RIZIV, 2023).

6.3. Step 2: clinical examination at the specialist

According to De Lepeleire et al. (163), 88.52% of the GPs refer the patient to a specialist for a second opinion or diagnostic classification or treatment[9]. Patients are mainly referred to the neurology department (79.18%) and the geriatrics department (60.07%). When these percentages were weighted based on the proportion of patients visiting either specialist, referral to a neurologist was 56.86% and to a geriatrist 43.14%. These percentages are later used for the weighted cost of a specialist consult. For the remaining 11.48% of patients, MCI was suspected, but no further testing was performed. Only patient management programs are a possible treatment option for these patients, as symptomatic treatment needs to be prescribed by a specialist.

To map the sensitivity and specificity values associated with a specialist, the values for the MMSE test in specialist settings were used: sensitivity of 71.10% and specificity of 95.60 (165).

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[9] In Belgium, some AD-specific medication is only reimbursed if prescribed by a specialist.

According to Nomensoft, the cost for consulting a neurologist is € 61.74, a geriatrist €38.08, and a neuropsychiatrist € 50.94. Because Belgian GPs usually do not refer to a neuropsychiatric, the associated costs of only a neurologist and a geriatrist were considered (163). Consequently, the weighted cost for a specialist consult was estimated at € 51.53. In the case of MCI, clinical examination by the specialist is supplemented by a neuropsychological assessment performed by a psychologist. However, no additional cost for the psychologist consult is included in the model.

6.4. Step 3: structural imaging

Structural imaging is necessary, mainly to exclude other reasons for cognitive decline. A GP can directly request an MRI or CT scan, but the specialist generally does this. The choice between an MRI or CT scan can depend on several aspects, such as the age of the patient or waiting times. Due to the lack of reliable data, a 50/50 distribution between MRI scans and CT scans was assumed.

According to Nomensoft, the cost for an MRI brain scan is €103.69, and the cost for a CT brain scan is € 102.66. Applying a 50/50 distribution, the weighted cost for this model is estimated at €103.18. The weighted MRI/CT sensitivity and specificity are estimated to be around 75.50% and 87%, respectively (sens/spec MRI: 71%/89% (166) and CT: 80%/85% (167)).

6.5. Step 4: functional imaging

Structural imaging can be supplemented in specialist centers by functional imaging tests, such as a PET scan or a CSF analysis of AD biomarkers (tau, p-tau, Aβ40/42, and the Aβ40/42 ratio). However, this is highly dependent on the center's resources and the willingness of the patient and the specialist to come to a differential diagnosis. Due to a lack of reliable data, it was assumed that a PET scan was performed in 95% of the cases. The weighted sensitivity/specificity for PET/CSF analysis is estimated to be around 86.05% and 91.60% (sens/spec PET: 86%/92% (168)and CSF: 87%/84% (169).

According to Nomensoft, the total cost for a PET scan is €197.29. Different sources were used for the cost of a CSF analysis on AD biomarkers, namely the request form of the Neurobiobank of the University of Antwerp and an expert opinion of Dr. Tim Van Langenhove of UZ Gent in collaboration with UZ Brussels. There, the analysis cost is €125 and €165 for the patient, respectively, but this only covers the analysis, and not, for example, the costs for the lumbar puncture and sample processing. The cost for a lumbar puncture can be found in Nomensoft and is estimated at around €40.21. Eventually, for the cost of a CSF analysis, the average cost of the two analyses (€125 and €165) was added up with the total cost of a lumbar puncture (€40.21), being €185.21.

Finally, to estimate the total cost of the functional imaging process (PET/CSF), the weighted cost of the two was taken, considering the 95/5 distribution, being €196.69.

6.6. PRS screening

The estimated sensitivity and specificity of PRS is 78% and 77%, respectively (41). KU Leuven, a consortium partner in this project, provided these preliminary inputs.

It is difficult to estimate the proportion of 65+ individuals with cognitive complaints who will undergo PRS screening. In a national screening program in Belgium for breast cancer in women between 50 and 69 years old, a screening coverage of 75% is recommended to reach an acceptable cost-effectiveness level. Still, approximately 60% of women get screened (170). **In the base case analysis for PRS screening, the assumption was made that 75% of the target population is screened**, but different proportions (25%, 50%, 60%, 75%, and 100%) were explored in the scenario analyses.

As it is not easy to understand the results of a PRS test and its possible consequences, it would be necessary to discuss this with a professional. Therefore, we assumed all patients who tested positive on a PRS test (i.e., high genetic risk for MCI) would consult a GP.

Lastly, the cost of a PRS test was assumed to be €100, which was based on literature (145) and expert opinion.