

POLYGENIC RISK SCORES

**Are ready for application in
routine cardiological practice (PRO)**

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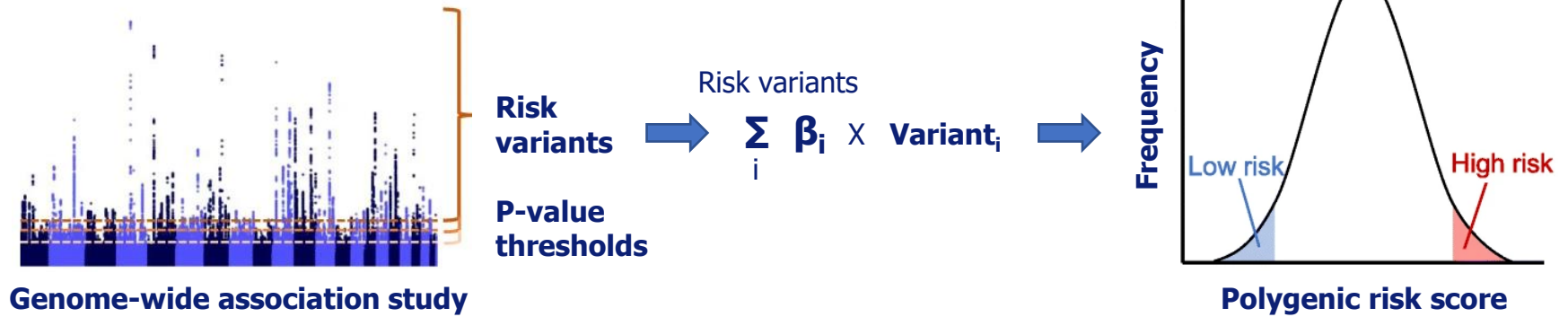
Epidemiology of Cardiometabolic Disorders

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Polygenic Risk Scores



The Clinical Utility of PRS

- In a clinical setting, the focus is on a single person
- What information does their PRS give about their risk of disease?
 - At what percentile in the distribution of PRS does this individual lie?
 - What is this person's relative risk of disease compared to the average risk in the population?
 - What is this person's absolute risk of disease, and by what age?

Lifeline of the Potential Relevance of PRS



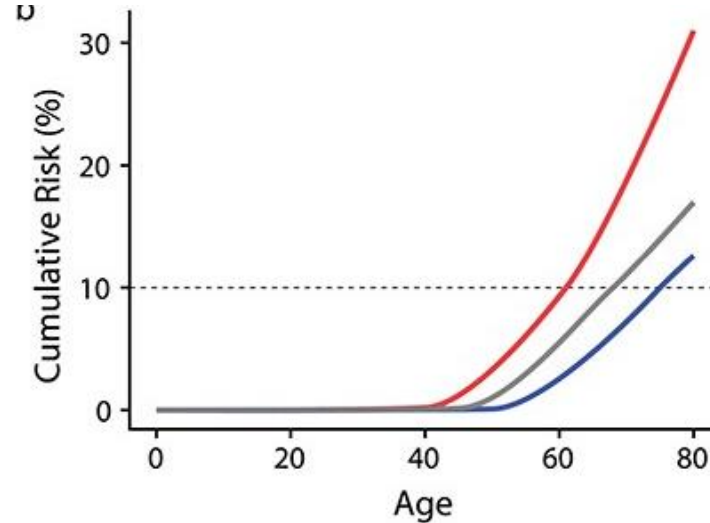
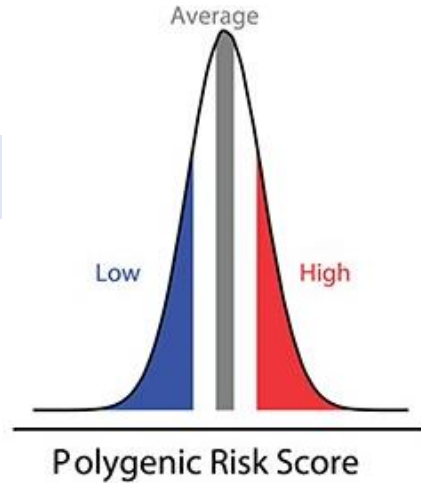
**From birth:
Risk prediction**

- PRS can be utilized earlier in life than can other (non-genetic) risk factors
 - Constructed on the basis of inherited genetic variation, set at conception
 - Despite fixed genetic liability, the risk arising from genes is dynamic, depending on changing factors such as age, environmental exposures, and previous illnesses.
- PRS provides the opportunity to estimate risk trajectories across a lifetime,
 - Rather than for 5 or 10 years, as is the case for most clinical risk scores

Lifeline of the Potential Relevance of PRS



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Risk prediction**

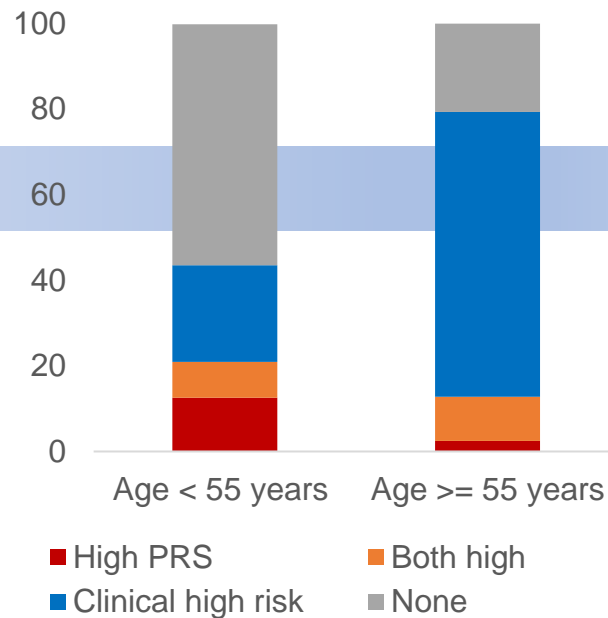
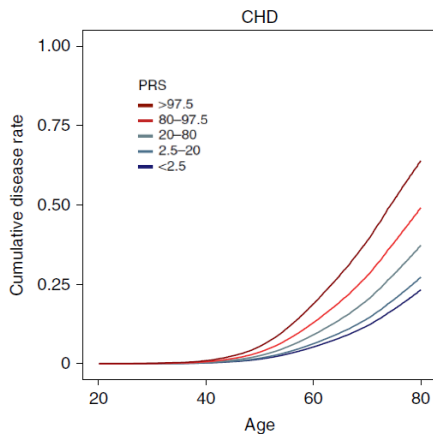


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Lifeline of the Potential Relevance of PRS



**From birth:
Risk prediction**



Proportions of early- and late-onset CHD cases with high clinical risk, high polygenic risk or neither

Lifeline of the Potential Relevance of PRS



**From birth:
Risk prediction**



**Early symptoms
Prodromal phase**

- Elevated genetic risk can be associated with earlier disease onset, even in the absence of traditional risk factors.
 - PRSs hold the potential to improve the accuracy of both early and targeted primary prevention
 - Useful to encourage healthy behavior throughout life, although lacking the experience on how
 - Particularly relevant for chronic diseases developing over decades



Lifeline of the Potential Relevance of PRS

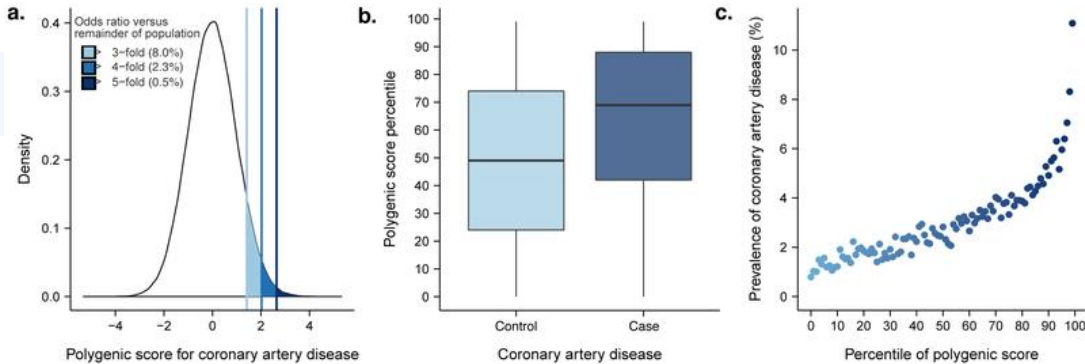


**From birth:
Risk prediction**

**Early symptoms
Prodromal phase**

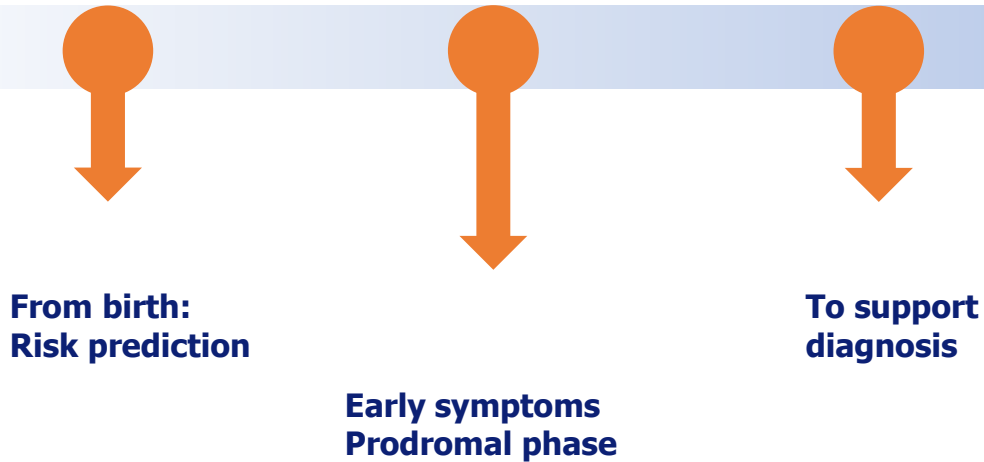
- Clinical utility:
 - Combined with non-genetic risk factors
 - PRS alone: for those with extremely high polygenic scores (i.e., top 8% of a CAD PRS distribution) have a risk comparable to that of those with a monogenic FH mutation
 - Availability of preventive interventions and/or medicine

Lifeline of the Potential Relevance of PRS



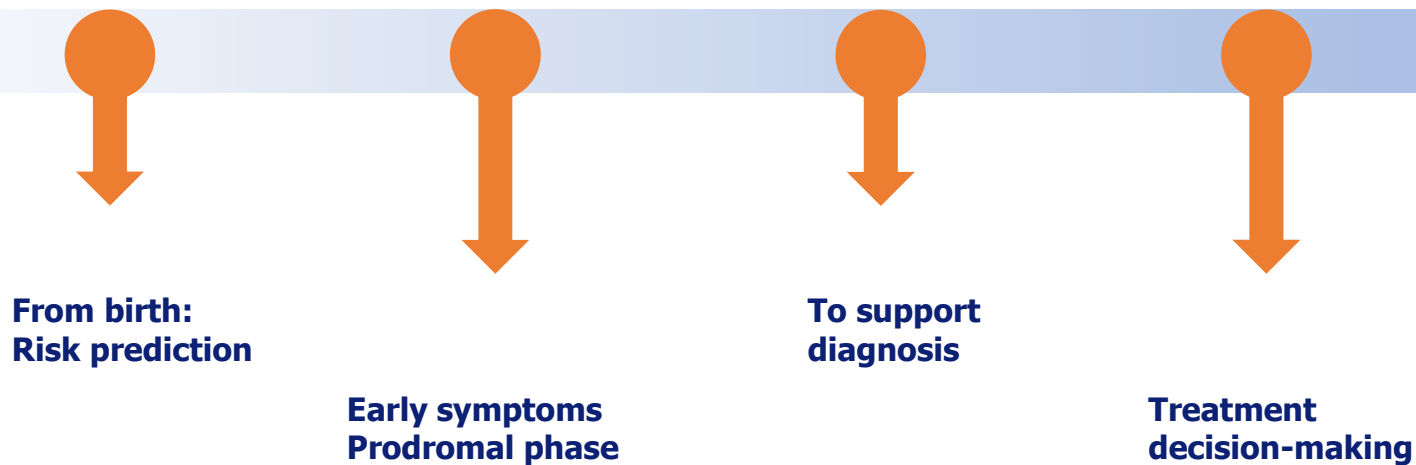
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Lifeline of the Potential Relevance of PRS

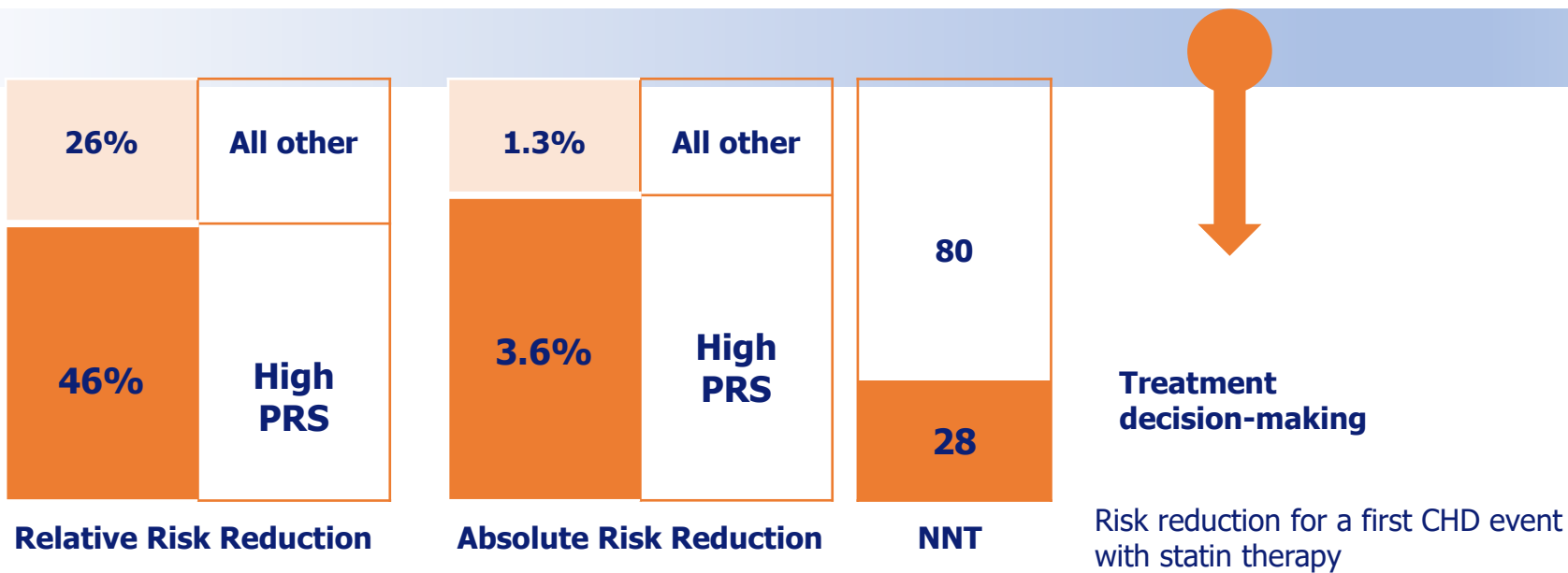


- PRS may improve diagnostic accuracy
 - Clinical differentiation between type 1 and type 2 diabetes can be complex
 - ~40% of individuals who develop T1D during their lifetime present with symptoms after the age of 30 years

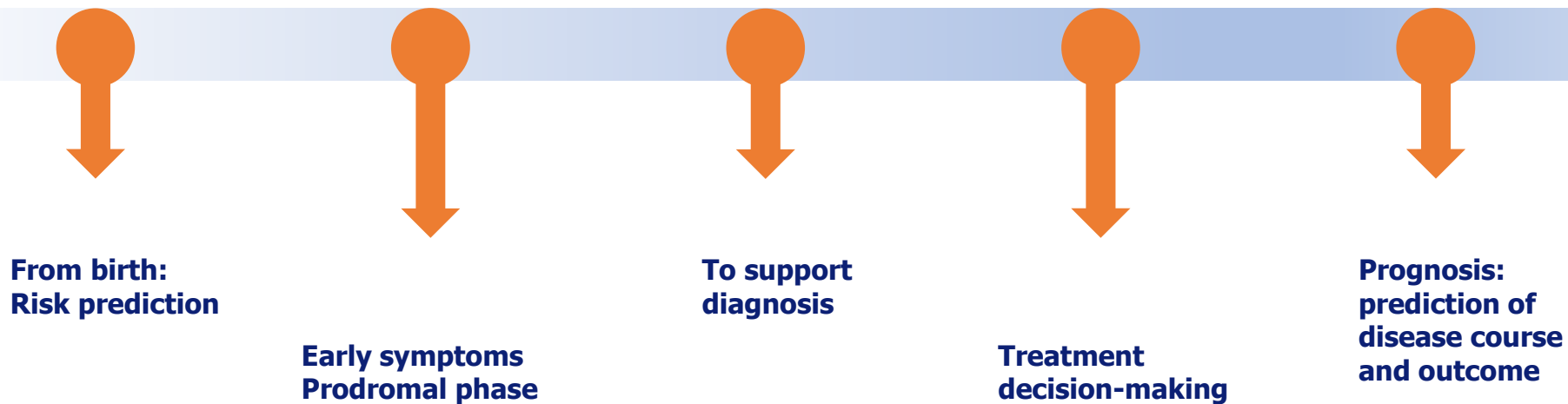
Lifeline of the Potential Relevance of PRS



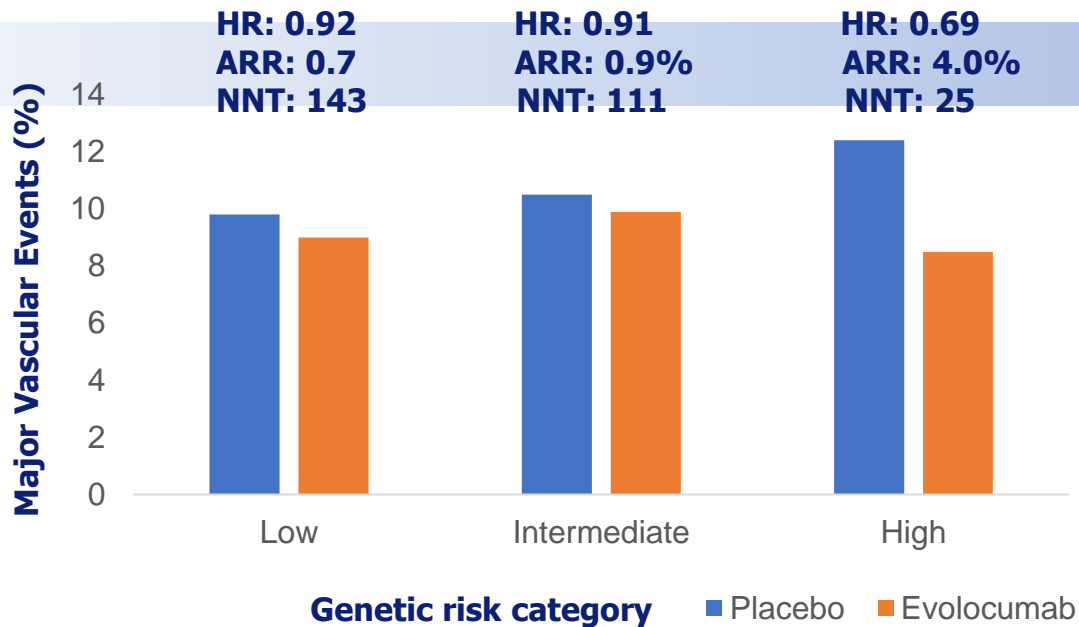
Lifeline of the Potential Relevance of PRS



Lifeline of the Potential Relevance of PRS

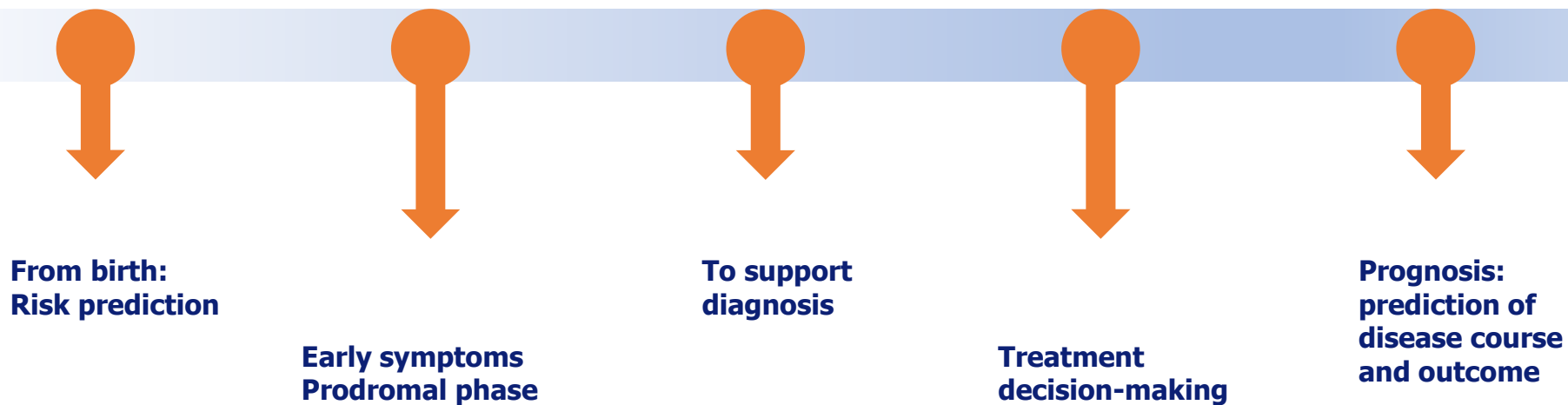


Lifeline of the Potential Relevance of PRS



Prognosis:
prediction of
disease course
and outcome

Lifeline of the Potential Relevance of PRS



Clinically Relevant PRS | Required Steps

- Realistic estimation of predictive ability in clinical populations
- Identification of the intended purpose of the PRS
- Recognition that even though not useful for the majority of the population (middle of the PRS distribution), may be relevant for those with high or low PRS (tails of the PRS distribution)
- Clarification if PRS has an additive or interaction effect with established epidemiological or biological risk factors before combining in joint prediction models
- Engagement of clinicians and service users, to ensure:
 - Avoiding application of PRS for deterministic interpretations
 - PRS is an indicator, not a precise measure

From birth:
Risk prediction

Prodromal phase

To support
diagnosis

To assist
decision-making

Prognosis:
prediction of
disease course
And outcome

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