

ETHICAL ISSUES IN AD PREVENTION TRIALS: GENETICS, BIOMARKERS AND TREATMENT RISKS

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Disclosures

Member of advisory board, DSMB, speaker or investigator with:

AbbVie, Affiris, Astra-Zeneca, Biogen, Eisai, Ever, GE Health Care, Lundbeck, Lilly, Merck, Merz, Novartis, Pfizer, Sanofi-Aventis, Servier

OUTLINE

- Mise en contexte
- Ethical issues
- Strategies to help

MISE EN CONTEXTE - 1

- Therapeutic research in AD is shifting to earlier stages because the underlying pathology may be more responsive to early treatments
- Research diagnostic criteria for AD in asymptomatic, MCI/prodromal and dementia stages have been proposed
- Data on biomarkers of AD at all stages are available, in early (familial) and late onset

MISE EN CONTEXTE - 2

- Genetic markers indicate higher risk for AD (ApoE4) and are diagnostic (PS1, PS2, APP)
- Biomarkers such as amyloid (+) using PET or CSF indicate higher risk for AD in asymptomatic and MCI stages, and are supportive for diagnosis in dementia stage
- A stratification of risks for AD is possible using all available information

MISE EN CONTEXTE - 3

- Different interventions against AD are possible, ranging from life style changes to immunotherapy, carrying different levels of risks for harm
- Risk levels for AD must be matched to the therapeutic risk-benefit ratios of specific interventions

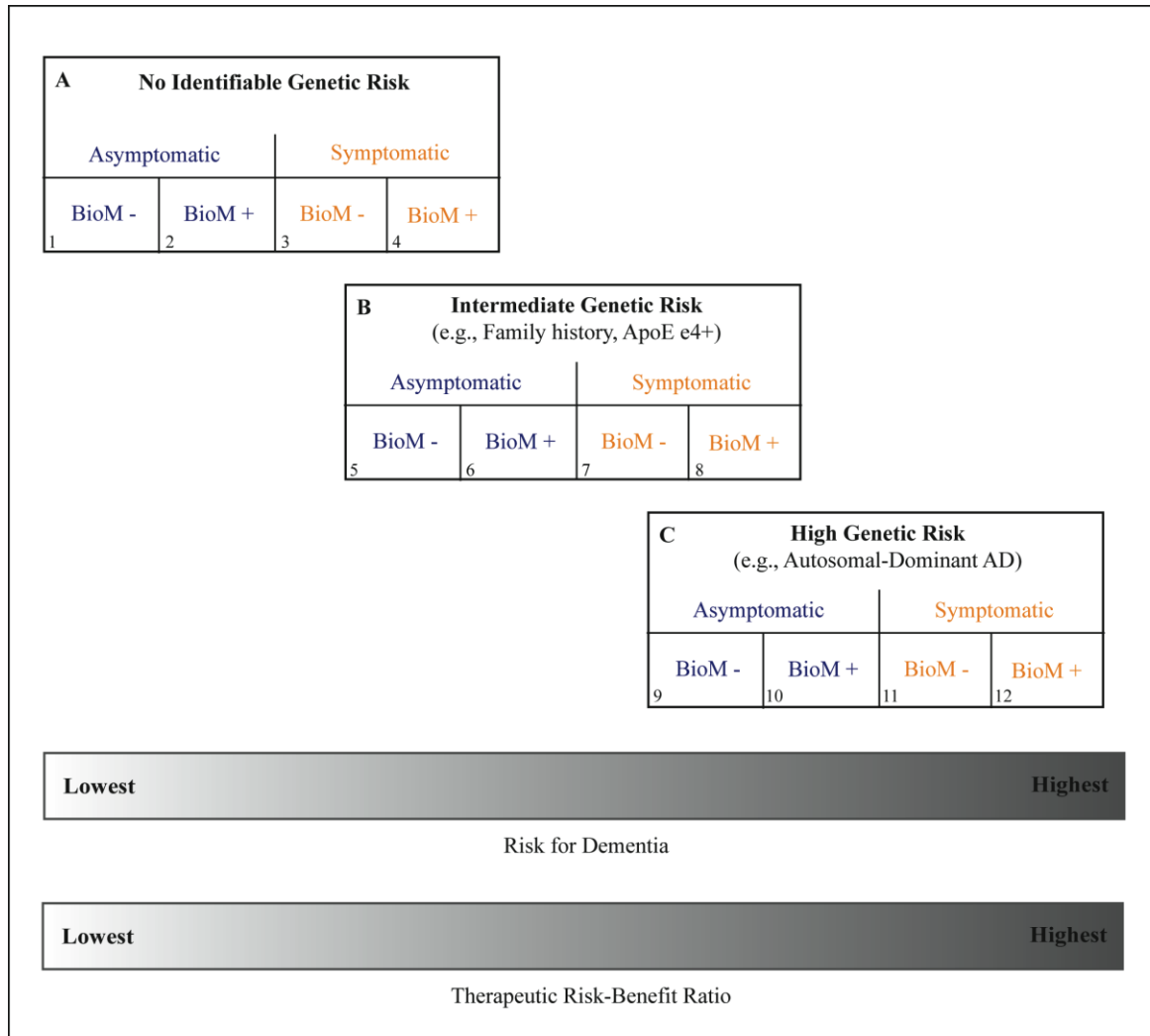


Figure 1: Conceptual framework anticipating AD prevention trials. Large samples (Boxes A, B, and C) are differentiated on the basis of genetic risk. The overlap between the three boxes is for heuristic purposes only and is not meant to imply any precise degree of risk. Groups within each box are differentiated by the presence of clinical symptoms (blue for asymptomatic and orange for symptomatic). Stratification illustrates individual status as positive or negative for biomarkers (BioM). The lower portion of the figure illustrates the degree of risk for dementia for the samples and groups. Superimposed on the framework are therapeutic risk-benefit ratios as a function of risk category.

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Special Issue: Neuroethics and Neurodegenerative Disease

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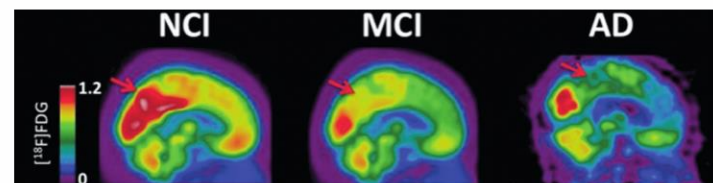


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PROGRESS IN NEUROBIOLOGY

Special Issue

Neuroethics and Neurodegenerative Disease



Guest Editors

Kevin Peters, B. Lynn Beattie and Judy Illes

OUTLINE

- Mise en contexte
- **Ethical issues**
- Strategies to help

CAIDE Dementia Risk Score

Age	< 47 years	0
	47-53 years	3
	>53 years	4
Formal education	≥10 years	0
	7-9 years	2
	0-6 years	3
Sex	Women	0
	Men	1
Systolic BP	≤ 140 mm Hg	0
	> 140 mm Hg	2
BMI	≤ 30 kg/m ²	0
	> 30 kg/m ²	2
Total cholesterol	≤ 6.5 mmol/l	0
	> 6.5 mmol/l	2
Physical activity	Active	0
	Inactive	1

**Kivipelto et
al., Lancet
Neurol 2006**

Probability of dementia in late-life according to the risk score category in middle age

The overall occurrence of dementia 4.4%

SCORE	All /Demented, n	% Risk (95% CI)
0-5	401 / 4	1.0 (0.0-2.0)
6-7	270 / 5	1.9 (0.2-3.5)
8-9	312 / 13	4.2 (1.9-6.4)
10-11	245 / 18	7.4 (4.1-10.6)
12-15	122 / 20	16.4 (9.7-23.1)

DISCLOSURE OF RISK SCORES

- Dementia Risk Score
- Derived from observational studies
- Used as entry criteria for intervention studies such as FINGER
- DRS score not disclosed during study

DISCLOSURE OF ApoE RESULTS IN THE API APOE ϵ 4 STUDY

- Asymptomatic subjects
- ApoE4/4 is an inclusion criteria
- All enrolled subjects will know of their homozygous status

DISCLOSURE OF AMYLOID TESTS RESULTS IN A4 STUDY

- Asymptomatic subjects
- Amyloid (+) is an inclusion criteria
- All enrolled subjects will know of their higher risk, they will be “PiB positive”

DISCLOSURE OF PS1, PS2, APP RESULTS IN DIAN-TU & API ADAD STUDIES

- Asymptomatic, MCI or mild dementia
- Known mutation in the family is a requirement
- Subjects agree not to know their individual results

OUTLINE

- Mise en contexte
- Ethical issues
- **Strategies to help**

STUDY-SPECIFIC STRATEGIES TO HELP WITH ETHICAL ISSUES IN AD PREVENTION TRIALS

- Committees within each study:

API genetic disclosure: R.Caselli, J.Karlawish, S.Kim, G.Marchant, B.McCarty Wood, S.Roberts

ADAD Ethics & Cultural sensitivity: J.Karlawish, S.Kim, K.Kosik, Y.Quiroz)

- Sub-studies looking at risks of disclosure

STUDY-SPECIFIC STRATEGIES TO HELP WITH ETHICAL ISSUES IN AD PREVENTION TRIALS

- Participants' involvement in study design (random allocation ratios), language of consent forms
- Role of DSMBs to monitor efficacy and futility

BROADER STRATEGIES TO HELP WITH ETHICAL ISSUES IN AD PREVENTION TRIALS

- Education of IRBs about risks for AD vs risks of intervention
- Advocacy role of potential participants
- National Biomedical Research Ethics Council (NBREC) as a North American IRB to examine large prevention trials and facilitate the work of local IRBs

BROADER STRATEGIES TO HELP WITH ETHICAL ISSUES IN AD PREVENTION TRIALS

- Knowledge transfer from trials to clinical practice, clinical utility of research findings, applicability to emerging countries should be considered throughout the prevention trials
- This may be facilitated by Ethical Legal and Social Impact (ELSI) committees for each major prevention trial

ELSI COMMITTEE IN THE Canadian Consortium for Neurodegeneration and Aging (CCNA)

- L. Beattie, J. Chandler, J. Fisk, S. Gauthier, T. Green, J. Illes, K. Jacklin, W. Lahey, E. Racine
- Support for NBREC – CCNA review as test case
- Study participants' perspectives in DIAN
- Monitor impact of disclosure of tests results in RCTs

CONCLUSIONS

- High ethical standards in current AD prevention trials, that will lead to guidelines for diagnostic and treatment management
- Our efforts for AD prevention should be balanced between non-pharmacologic low tech trials for lower risk populations as well as pharmacologic high tech trials for high risk populations