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Modeling disease-modifying treatments in MCI and early-stage AD patients using health economic microsimulations

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***NOTE**: This work has been funded by the National Institute on Aging, awards P30AG024968 and R01AG062277.*

Multiple possibly disease-modifying therapies for MCI and early AD are in the pipeline

Drug developers have achieved promising results in Phase 2 and Phase 3 trials; first possibly disease-modifying therapy (DMT) was approved in June for MCI and early AD in the U.S.

DMT trialists often use a range of endpoints for effectiveness – those are typically in **biomarker, cognitive, functional, behavioral and global** domains

We need models to understand the benefits and policy implications of emerging DMTs in AD and MCI outside of trial context

- Trials run for short durations only, not representative, do not measure all relevant outcomes
- Preparedness is key given large population pools and significant disease burden

Key characteristics of emerging AD DMTs

- **Three drug candidates in the review process in the U.S.**
  - **Aducanumab** (Biogen) received **accelerated approval** in June 2021 (based on biomarker benefit, validation of clinical benefit ongoing until 2029)
  - **Lecanemab** - BAN2401 (Biogen/Eisai) – initiated **rolling submission** to the FDA for accelerated approval in September 2021 (based on Phase 2b data)
  - **Donanemab** (Eli Lilly) **submitted application to FDA for accelerated approval** in October 2021 (based on Phase 2 results, biomarker benefit only)
- **Many others in different phases** (e.g. Cummings et al. 2020 and older) **and different therapeutic approaches** (e.g. Aisen et al., 2020)

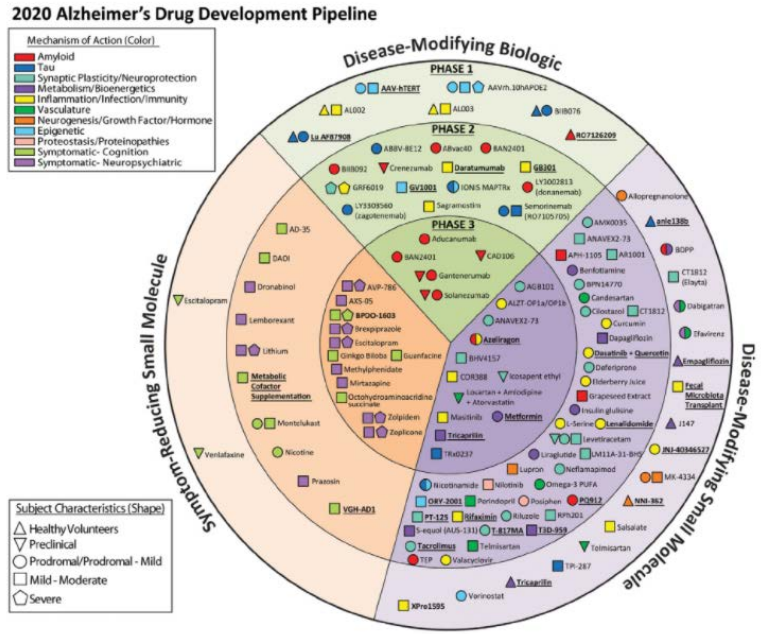


FIGURE 1 Agents in clinical trials for treatment of Alzheimer's disease in 2020 (from ClinicalTrials.gov as of February 27, 2020. The inner ring shows Phase 3 agents; the middle ring is comprised of Phase 2 agents; the outer ring presents Phase 1 compounds; agents in green areas are biologics; agents in purple are disease-modifying small molecules; agents in orange areas are symptomatic agents addressing cognitive enhancement or behavioral and neuropsychiatric symptoms; the shape of the icon shows the population of the trial; the icon color shows the class of target for the agent. Agents underlined are new to the pipeline since 2019 (Figure by Mike de la Flor)

Source: Cummings et al. (2020)
https://alz-journals.onlinelibrary.wiley.com/doi/epdf/10.1002/trc2.12050

https://healthpolicy.usc.edu/research/prospects-for-future-advances-in-alzheimers-disease/

Implications of trial design choices for modeling

Select Pivotal Trials

	Age Range (Trials)	Cognitive Level	Key Exclusions in Trial	Dosing	Primary Endpoint(s)	Notes
Aducanumab (Biogen)	50 - 85	**MCI and early AD** CDR 0.5, MMSE 24-30, positive PET	Any other neurological condition, recent history of TIA/angina/MI/HF, unstable psychiatric illness/substance abuse, impaired renal/liver function	1x monthly	CDR-SB at week 78	FDA approved for MCI and mild AD
Lecanemab - BAN2401 (Biogen/Eisai)	50 – 90	**MCI due to AD** CDR 0.5 or 1, episodic impairment, positive PET/CSF, MMSE 22+	Any other neurological and psychiatric condition, history of TIA, depression, ECG abnormality	1x monthly	ADCOMS* in Phase 2 CDR-SB in Phase 3	Phase 2 (Phase 3 also underway)
Donanemab (Eli Lilly)	60 – 85	**MCI and early AD** MMSE 20-28, positive PET	History of ECG abnormality, contraindication to MRI	1x monthly	ADAS-Cog13, ADCS-ADL, MMSE, CDR-SB in Phase 2, iADRS** at week 78 in Phase 3	Phase 2 (Phase 3 also underway)
Gantenerumab (Roche/Chugai)	50 – 90	**Probable and prodromal AD** MMSE 22+, positive PET/CSF, CDR 0.5 or 1	Any other neurological and psychiatric condition, (cerebro)vascular disease, history of stroke, CNS trauma, intracranial mass, autoimmune disorder, substance abuse, other diseases	1x monthly	CDR-SB at 2 years	Phase 3

*__ADCOMS__ consists of 4 Alzheimer's Disease Assessment Scale–cognitive subscale items, 2 Mini-Mental State Examination items, and all 6 Clinical Dementia Rating—Sum of Boxes items

Different primary endpoints across AD DMT trials

- **We reviewed 314 trials in AD (1996-2020), 39.5% possibly DMTs**
  - 50.6% had 1 primary endpoint
  - 35.7% had 2 primary endpoints
  - 7.3% had 3 primary endpoints
  - 4.8% had 4 or 5 primary endpoints
- **Most common non-biomarker endpoints:**

COGNITIVE	– Alzheimer's Disease Assessment Scale – Cognitive Subscale (**ADAS-Cog**): 145 trials – Mini-Mental State Examination (**MMSE**): 45 trials – Severe Impairment Battery (**SIB**): 24 trials
BEHAVIORAL	– Neuropsychiatric Inventory (**NPI**): 35 trials – Cohen-Mansfield Agitation Inventory (**CMAI**): 19 trials
FUNCTIONAL	– Alzheimer's Disease Cooperative Study – Activities of Daily Living (**ADCS-ADL**): 33 trials
HYBRID/ GLOBAL	– Clinician's Interview-Based Impress of Change – Plus Caregiver Input (**CIBIC+**): 36 trials – Clinical Global Impression of Change (**CGIC**): 21 trials – Clinical Global Impression (**CGI**): 16 trials – Clinical Dementia Rating Scale – Sum of Boxes (**CDR-SB**): 30 trials

... and others (144 unique primary endpoints identified)

Mapping trial endpoints to model outcomes

- **Economic models may use different endpoints or not use trial endpoints at all (e.g. use relative risk, RR)**
  - Where similar endpoints are used (e.g. measuring cognitive decline using MMSE vs. CDR), **crosswalks may be necessary (see our *review article*)**
  - Where non-endpoint approaches are used, **careful translation of trial endpoints to transition probabilities (RR) is necessary** (may require ranges, scenario building)
- **Domain-specific modeling may be preferable**
  - E.g. an equivalent treatment effect in the cognitive domain is unlikely to yield same outcomes as a treatment effect in the functional domain
    - Modeling multiple domains at once may lead to the **risk of double counting**
  - **Few models model specific domains – examples:**
    - Future Elderly Model (USC)
    - IPECAD open-access model
    - Herring model (RTI)
    - others

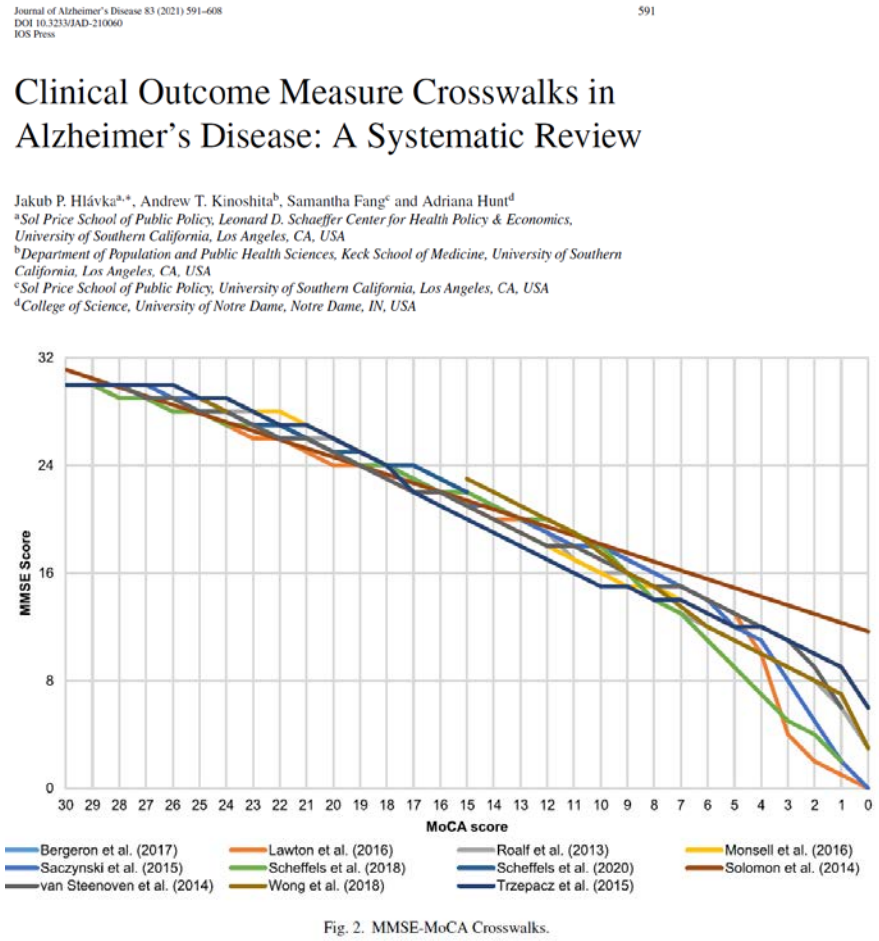
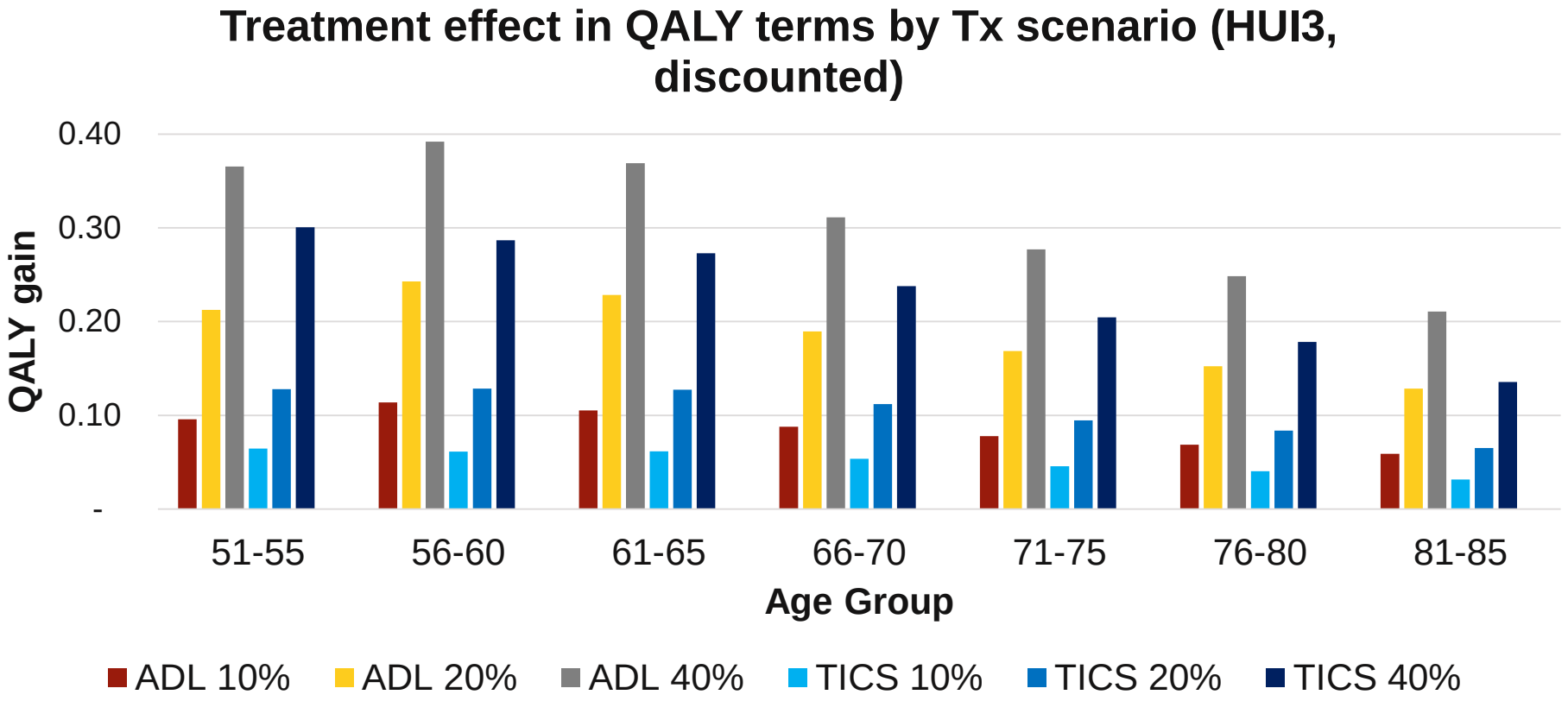


Fig. 2. MMSE-MoCA Crosswalks.

Clinical Outcome Measure Crosswalks in Alzheimer's Disease: A Systematic Review
Hlávka et al., 2021
https://pubmed.ncbi.nlm.nih.gov/34334392/

Large differences in effectiveness by age and treatment scenario (example from FEM modeling)



Preliminary results

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Key model considerations and assumptions

- Treatment-eligible populations
  - **Demographic characteristics** (age, gender, race, ... – trials often struggle with representative enrollment in non-white populations)
  - **Inclusions and exclusions** (disease stage, comorbid conditions ...)
  - **Baseline decline in control group** (trial participants may not mirror average disease progression due to selection issues)
- Treatment effectiveness
  - **Type of treatment effect** (e.g. domain-specific, risk reduction etc.)
  - **Length of treatment** (stopping rules/discontinuation)
  - **Length of effectiveness** (trial duration only, extrapolated, tapered etc.)
  - **Response rate** (probability of response to treatment)
- Side effects
  - **Minor adverse events** (not resulting in discontinuation)
  - **Major adverse events** (stopping rule, health and economic consequences)

Ongoing relevant work

- **Analyzing future treatment paradigms in AD**
  - Review of clinical trials, trial design choices and likely effectiveness bounds
- **Developing and validating relevant crosswalks**
  - MMSE and TICS-27/30/40 crosswalk
  - CDR-SB modeling
- **Estimating treatment eligible patient populations**
  - Using HRS, genetic status and specialist capacity to estimate numbers of patients who may present to care for AD DMTs
- **Cost-effectiveness of future AD DMTs**
  - Use FEM to model different treatment effectiveness scenarios and indicate cost-effectiveness under key assumptions in different patient populations

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NOTE: This research is under review – results are not to be disseminated without permission. *This work was funded by the National Institute on Aging, awards P30AG024968 and R01AG062277.*

Conclusions

- **Trial results do not always offer direct inputs to models**
  - New tools (e.g. crosswalks) are needed to overcome this challenge
- **Assumptions of models should be transparent**
  - Large variation in outcomes by age, treatment groups etc.
- **Ongoing work (including crossvalidation (IPECAD) and modeling of AD DMTs by research groups)** can indicate the range of possible health and policy outcomes
  - Research collaboration is important as new AD DMTs emerge
  - Need to communicate the uncertainty of modeled outcomes to the broader public