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Treating Alzheimer Disease with lecanemab:
The Washington University experience

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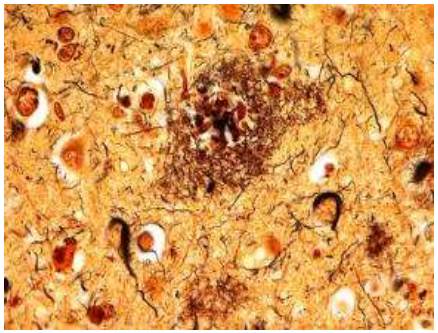
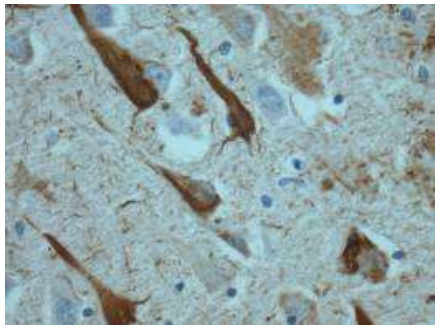
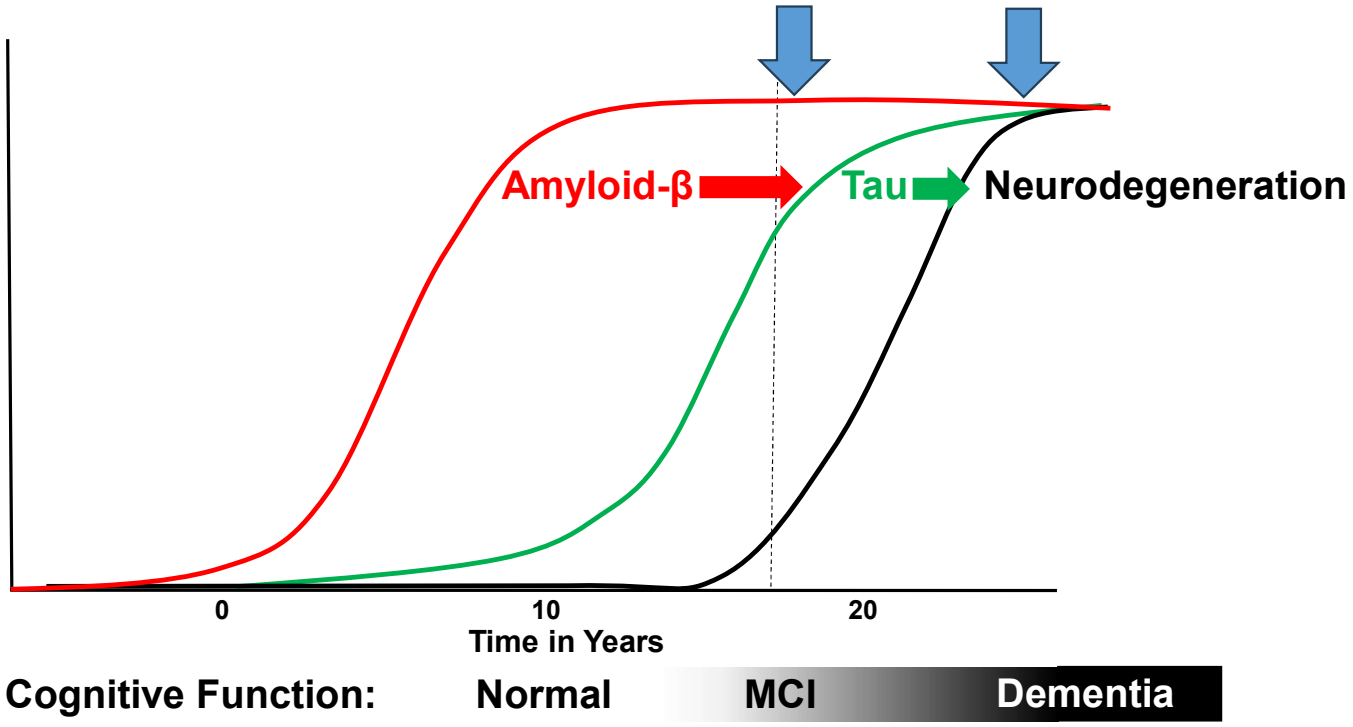
Amyloid-β in Alzheimer's Disease Pathogenesis

Amyloid plaque (Aβ)



Neurofibrillary tangle (tau)

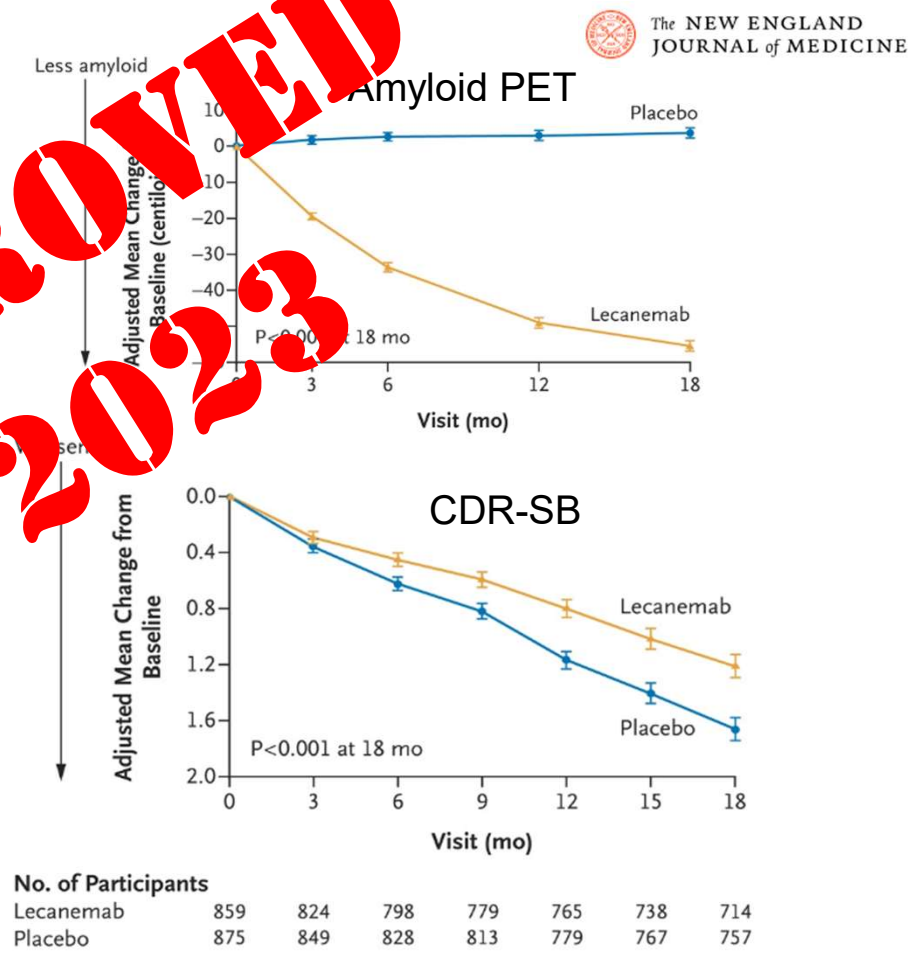




Lecanemab meets primary endpoints in phase III trial

- Phase III trial of MCI and mild AD
  - N=874 placebo, N=859 lecanemab
  - 18 months treatment
  - CDR 0.5 or 1, MMSE
- Strong amyloid plaque removal
  - CSF p-tau also lower
- **Significant slowing of cognitive decline across scales.**
  - 27% slowing of CDR-SB decline
  - Met primary endpoint

FDA APPROVED JULY 2023



Van Dyck et al, *NEJM*, 2022

ARIA is a major side effect of lecanemab

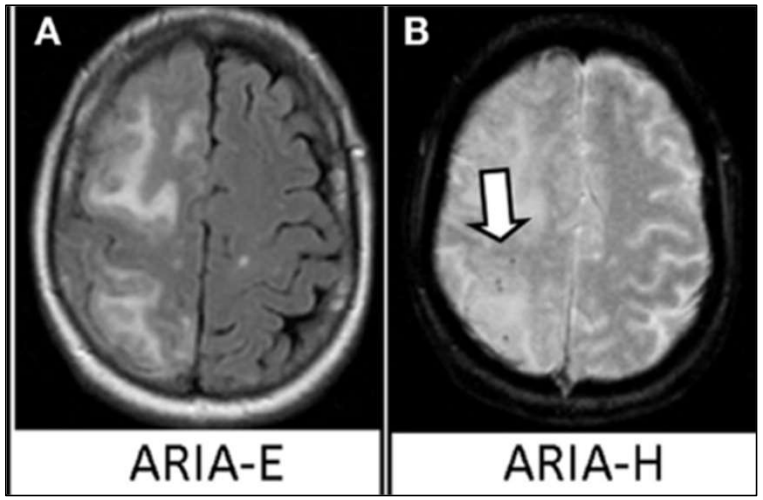


Table 3. Adverse Events.*

Event	Lecanemab (N=898)	Placebo (N=897)
ARIA‡		
ARIA-E — no. (%)	113 (12.6)	15 (1.7)
Symptomatic ARIA-E — no. (%)§	25 (2.8)	0
ApoE ε4 noncarrier — no./total no. (%)	4/278 (1.4)	0/286
ApoE ε4 carrier — no./total no. (%)	21/620 (3.4)	0/611
ApoE ε4 heterozygote	8/479 (1.7)	0/478
ApoE ε4 homozygote	13/141 (9.2)	0/133
ARIA-E according to ApoE ε4 genotype — no./total no. (%)		
ApoE ε4 noncarrier	15/278 (5.4)	1/286 (0.3)
ApoE ε4 carrier	98/620 (15.8)	14/611 (2.3)
ApoE ε4 heterozygote	52/479 (10.9)	9/478 (1.9)
ApoE ε4 homozygote	46/141 (32.6)	5/133 (3.8)
ARIA-H — no. (%)	155 (17.3)	81 (9.0)
Microhemorrhage	126 (14.0)	68 (7.6)
Superficial siderosis	50 (5.6)	21 (2.3)
Macrohemorrhage	5 (0.6)	1 (0.1)
Symptomatic ARIA-H§	6 (0.7)	2 (0.2)
Isolated ARIA-H: no concurrent ARIA-E	80 (8.9)	70 (7.8)
ARIA-H according to ApoE ε4 genotype — no./total no. (%)		
ApoE ε4 noncarrier	33/278 (11.9)	12/286 (4.2)
ApoE ε4 carrier	122/620 (19.7)	69/611 (11.3)
ApoE ε4 heterozygote	67/479 (14.0)	41/478 (8.6)
ApoE ε4 homozygote	55/141 (39.0)	28/133 (21.1)
ARIA-E or ARIA-H — no. (%)	193 (21.5)	85 (9.5)
Concurrent ARIA-E and ARIA-H — no. (%)	74 (8.2)	9 (1.0)

Van Dyck et al, *NEJM*, 2022

How do we treat with lecanemab?

Patients with similar characteristics as those enrolled in CLARITY-AD:

- MCI or mild, symptomatic AD: CDR 0.5, MMSE 22+
- Biomarker evidence of amyloid: CSF $pTau_{181}/A\beta_{42}$ ratio, Amyloid PET+, PrecivityAD2+
- Recent MRI (within 12mo) with <4 microhemorrhages, no siderosis, no active lesions
- Able to tolerate/get multiple MRIs
- No other major, active medical problems (renal failure, cirrhosis, severe CHF, active cancer…)
- *ApoE4/4 - increased risk of ARIA based on CLARITY-AD data, discuss risk/benefit.
- *Anticoagulation- theoretical increased risk of hemorrhage, not shown in CLARITY-AD, discuss risk/benefit.

These criteria are based on best practices considering the limited data we have now, are likely to change over time.

Many/most current AD patients are not eligible based on these criteria (~25%)

The Patient Journey to Lecanemab at WashU

Patient referred to WashU Memory Diagnostic Center (MDC)
- Referral from primary care provider or general neurologist

Initial 1hr visit with MDC Neurologist (Dementia specialist) 100%
- 30-45 minute discussion with collateral source (spouse, child, friend, etc)
- Psychometric battery (Boston naming, MMSE, SBT, Trail A/B, Logical memory, etc)
- Review of medical history, medications, any labs/imaging
- Clinical Dementia Rating (CDR) is determined.
- May initiate preliminary discussion of AD biomarkers and lecanemab

Complete/review initial dementia workup ~80-90%
- Brain MRI (dementia protocol- evaluate brain volume and any ARIA)
- Labs: vitamin B12, thyroid tests, general liver/kidney/infection panels.

Alzheimer Disease Biomarker testing ~30-40%
- CSF Aβ42, tau, pTau181; Amyloid PET, Plasma PrecivityAD2 (pTau271, Aβ42/40)
- ApoE genotype/proteotype (to evaluate for ApoE4/4)

The Patient Journey to Lecanemab at WashU, cont.

Alzheimer Disease Biomarker testing shows amyloid pathology ~25%

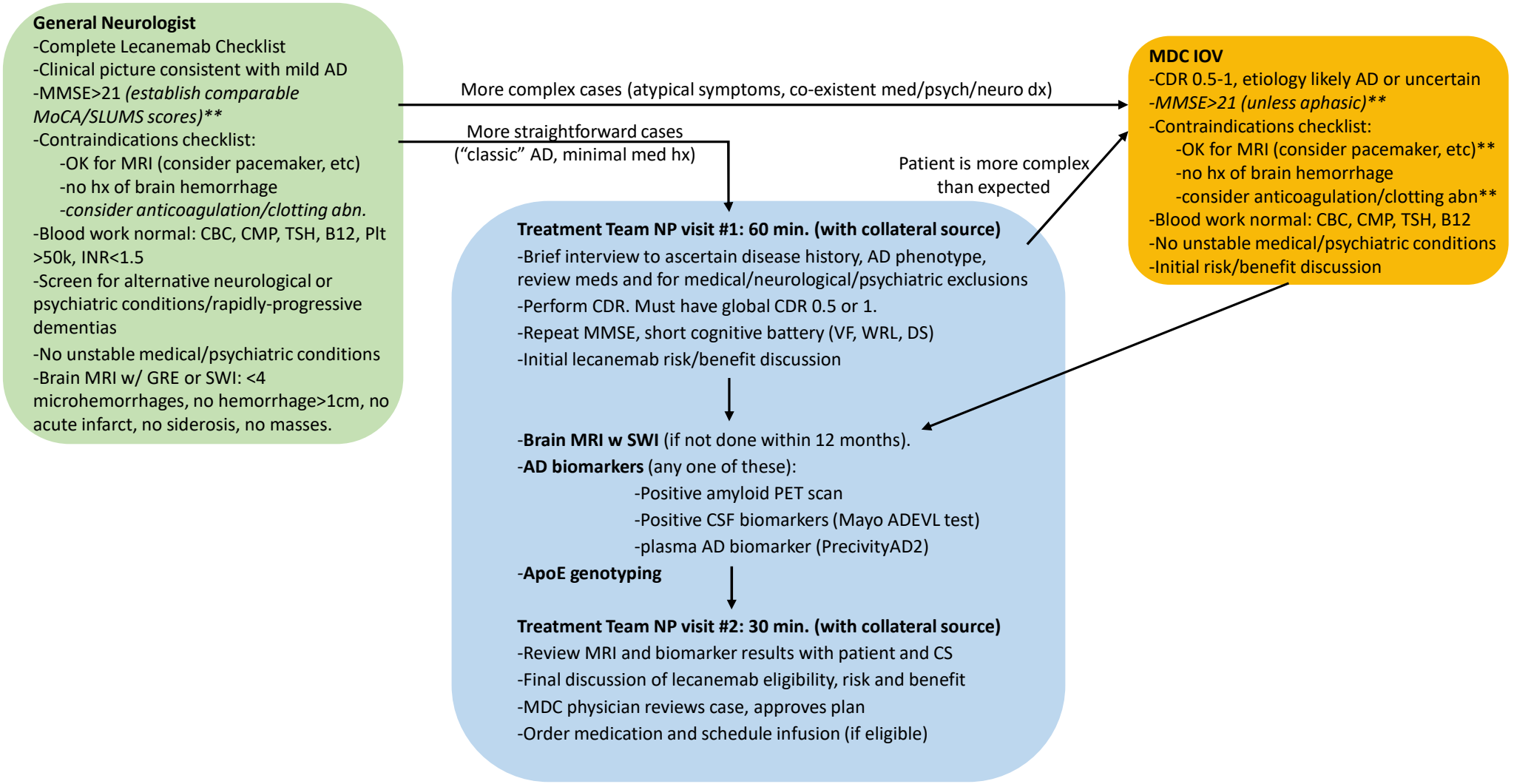
Discussion about lecanemab with patient and family ~25%
Clear discussion of risk and realistic understanding of benefits. Informed consent.
Consider impact on lifestyle, access to infusion/MRI facilities, insurance/resources

Patient wants to proceed ~15-20%

- CMS Registry completed (provider)
- Lecanemab ordered (provider)
- Insurance precertification (office staff)
- Infusions and MRIs (3 in total) are scheduled (office staff)

Patient referred to lecanemab treatment team
- Review MRIs prior to next infusion
- Address isses related to infusions
- 6mo followup for repeat psychometrics, exam

WashU Memory Diagnostic Center (MDC) Lecanemab Algorithm



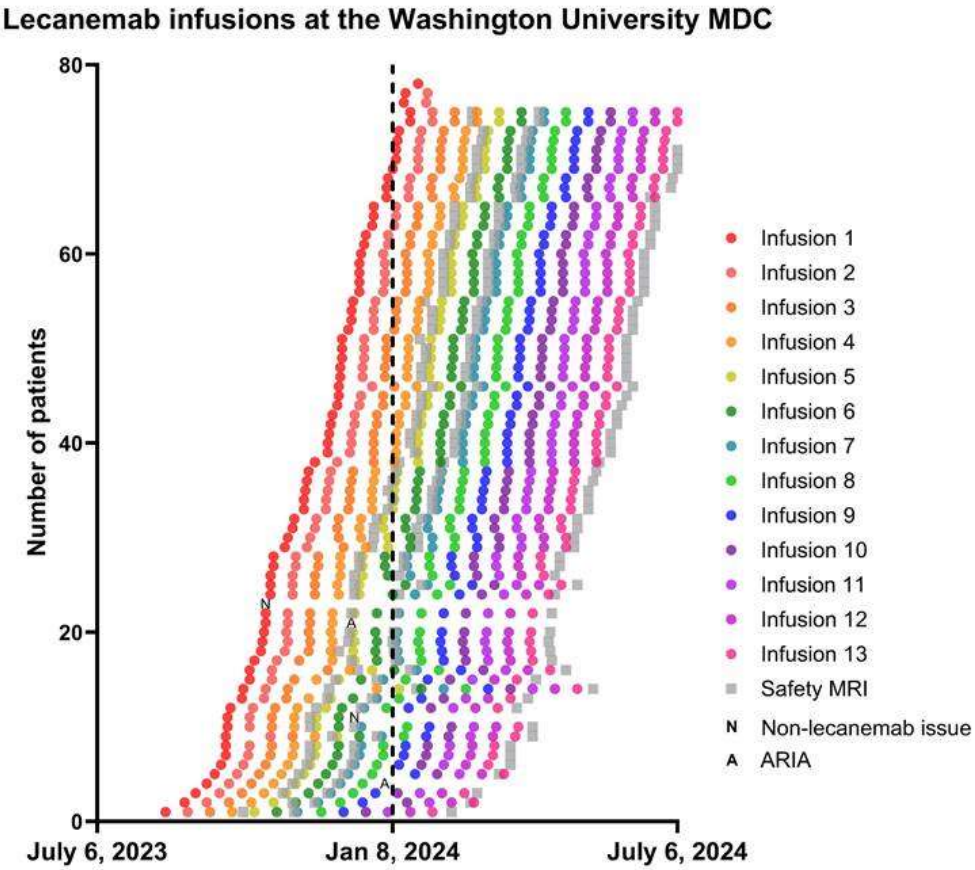
Special clinical requirements

- Dementia-trained neurologists, nurse practitioners, and PAs
- MRI capacity and neuroradiologists trained to detect ARIA
- Biomarker capabilities (lumbar puncture clinic, amyloid PET facilities, understanding of how to evaluate results).
- Support staff to coordinate infusion scheduling, MRIs (to be sure they are read on time), ensure all “boxes are checked”
- Infusion center capacity

- Extremely work and resource intensive!

Our experience at WashU thus far…

- FDA approval July 6, CMS approval in parallel. First infusions at WashU in August 2023
  - Large backlog of pre-selected patients awaiting approval
- Demand for infusions and MRIs accumulates very quickly
- Entire existing staff now contributing to lecanemab effort, 2 new NPs hired specifically for lecanemab clinic.



Early challenges for our patients

- Access to MDC for initial evaluation (6-8 months waitlist)
- Proximity/accessibility of infusion centers, MRI
  - Distance from St. Louis area, availability of transportation
- Insurance coverage/cost
  - ApoE testing, plasma biomarkers not covered, many non-medicare (younger) patients not covered, traditional Medicare only covers 80%.
- Differentiating symptomatic ARIA from other common symptoms
  - Headache, dizziness, confusion are common in this population.

Key unanswered clinical use questions

- How long do we treat with lecanemab?
  - Can we stop when plaques are cleared? Then what?
- Do we need biomarkers to demonstrate plaque clearance?
  - Can we assume it's working in everyone?
- Are disruptions in the treatment schedule OK?
  - The problem of snowbirds and other travelers, other disruptions
- Is it safe to treat anticoagulated patients? ApoE4/4?
- Will registries prove helpful? How?

- Many other research questions: Long term effects? How to identify best candidate? Predict ARIA? Prevent ARIA? Optimize delivery? Optimize plaque clearance? Effects of mixed pathology…