Research Registries to Accelerate Enrollment in Alzheimer's Trials

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If I have seen further, it has been by standing on the shoulders of giants*

Jessica Langbaum
& her Alzheimer's Prevention Registry Team

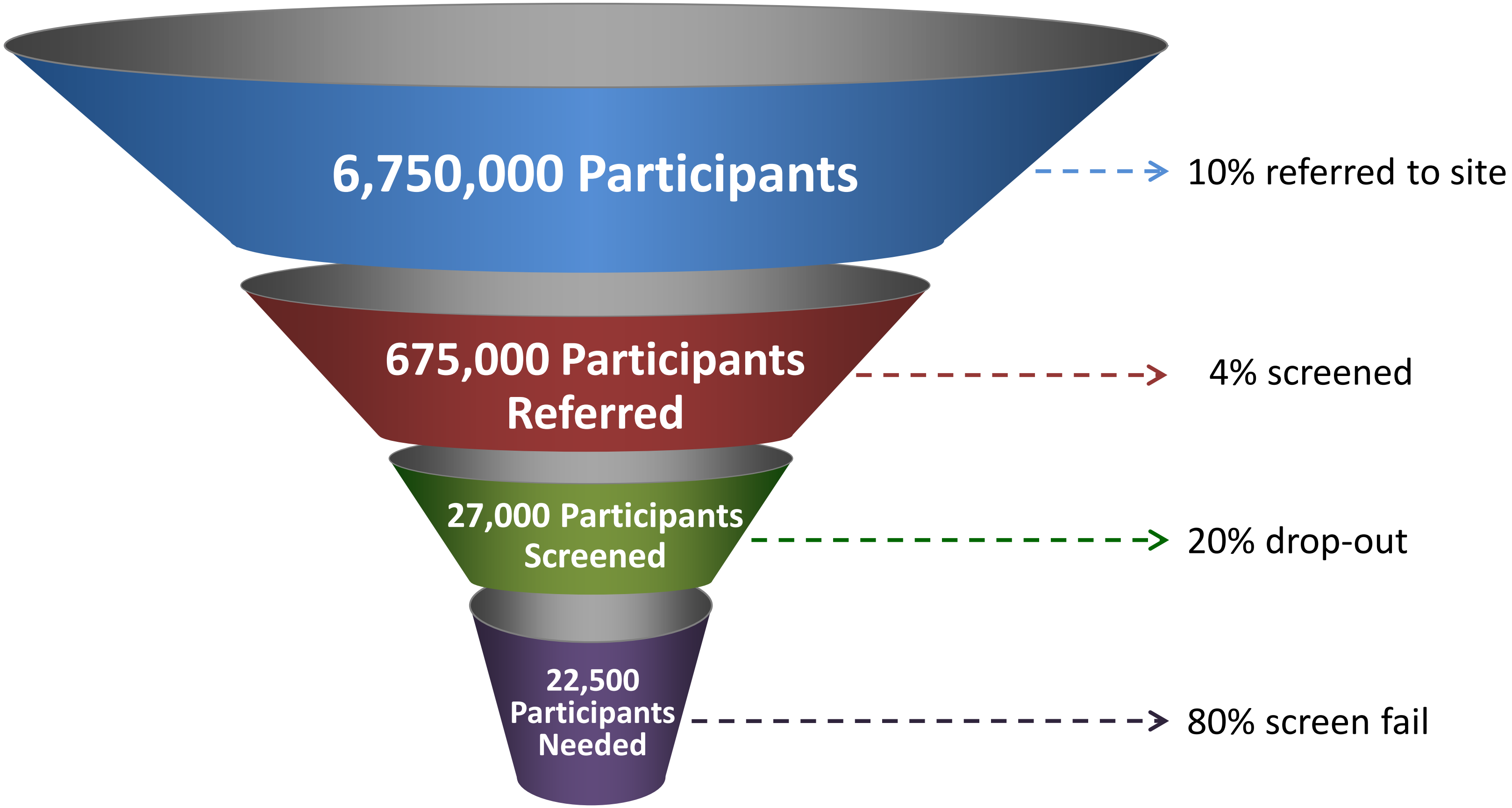
**Sir Isaac Newton*

AD Trial Enrollment: The Current US Landscape

- One needs to engage an extraordinary number of people to enroll a sufficient number of eligible participants in AD trials
- AD trials face a narrow, rate-limiting screening & enrollment funnel
  - Need to screen **tens of thousands** to identify the eligible thousands
  - Screen failure rates as high as 85%
- 93% of sites fail to meet their enrollment goal in the originally stated timeline
- 85-90% of all trials (not just AD) experience delays in recruitment & enrollment
- 30% of all trials fail to meet their enrollment goals

Current Recruiting Models Cannot Supply Enough AD Trial Participants*

To recruit the estimated 4,500 participants needed in 2016, nearly 7 million people should be contacted



6,750,000 Participants

10% referred to site

675,000 Participants Referred

4% screened

27,000 Participants Screened

20% drop-out

22,500 Participants Needed

80% screen fail

4,500 Participants Randomized

courtesy of GAP Foundation

Why a Registry?

- Able to reach thousands of interested individuals for a potential study
- If eligible, able to re-contacted later for a different study
- Potential to accelerate trial enrollment & perhaps enhance retention
- Potential to reduce screen failure rate
- Online registry can complement & enhance local, grassroots recruitment
- Depending on registry's design, may be able to leverage run-in data for trial

General Public Perceptions about Research Registries

- We analyzed nearly 19,000 conversations from 84 online destinations (websites, blogs, forums, etc.) to try to understand the primary motivators & barriers to join a registry & participate in a trial
  - Drivers: helping future generations, driving science forward, taking control of their own lives
  - Barriers: concerns regarding privacy, data security, who is “behind” the program
- Meantime, we continue to learn from API & other programs about factors that influence a registry participant’s willingness to participate in a trial
  - e.g., their proximity to a trial site

Recruitment Registries: Examples in the US*

- **National Registries**
    - Alzheimer's Prevention Registry
    - Brain Health Registry
    - DIAN Expanded Registry
    - GeneMatch
    - HealthyBrains
    - ResearchMatch
    - TrialMatch

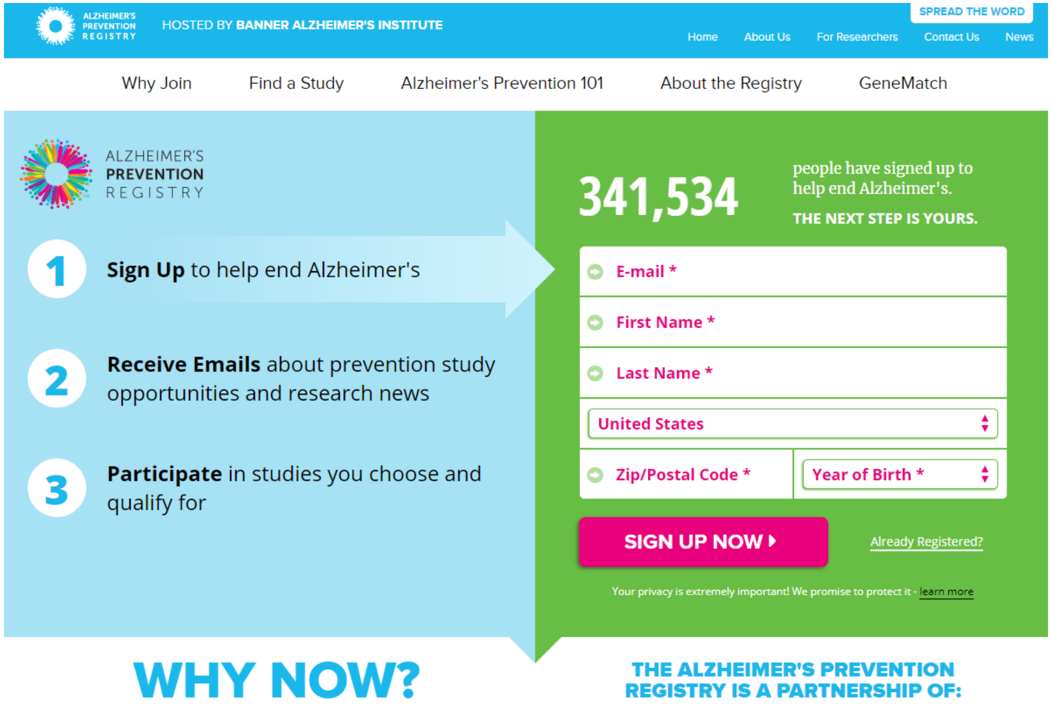
- **Local / Regional Registries**
    - Butler Alzheimer's Prevention Registry
    - Penn Memory Center Brain Health Research Registry
    - Rhode Island AD Prevention Registry
    - UC Irvine Consent-to-Contact Registry
    - Wisconsin ADRC Registry

Registries are listed in alphabetical order. Other registries may be found on clinicaltrials.gov

Tiers of Engagement in Several National Registries

Requirements / Engagement Tiers	Alzheimer's Prevention Registry	Brain Health Registry	GeneMatch	TrialMatch
consent / create account		X	X	X
contact Information	X	X	X	X
demographic information	X	X	X	X
study opportunity notifications	X	X	X	one-time match continuous match TBD
cognitive testing every 6 mos		X		
study partner Enrollment		optional		
DNA APOE tests			X	
DNA multiple genetic tests		GenePool substudy		
DNA storage for future tests		GenePool substudy		

Recruitment Registry Example: the Alzheimer's Prevention Registry



1 **Sign Up** to help end Alzheimer's

2 **Receive Emails** about prevention study opportunities and research news

3 **Participate** in studies you choose and qualify for

341,534 people have signed up to help end Alzheimer's.

THE NEXT STEP IS YOURS.

Your privacy is extremely important! We promise to protect it - learn more

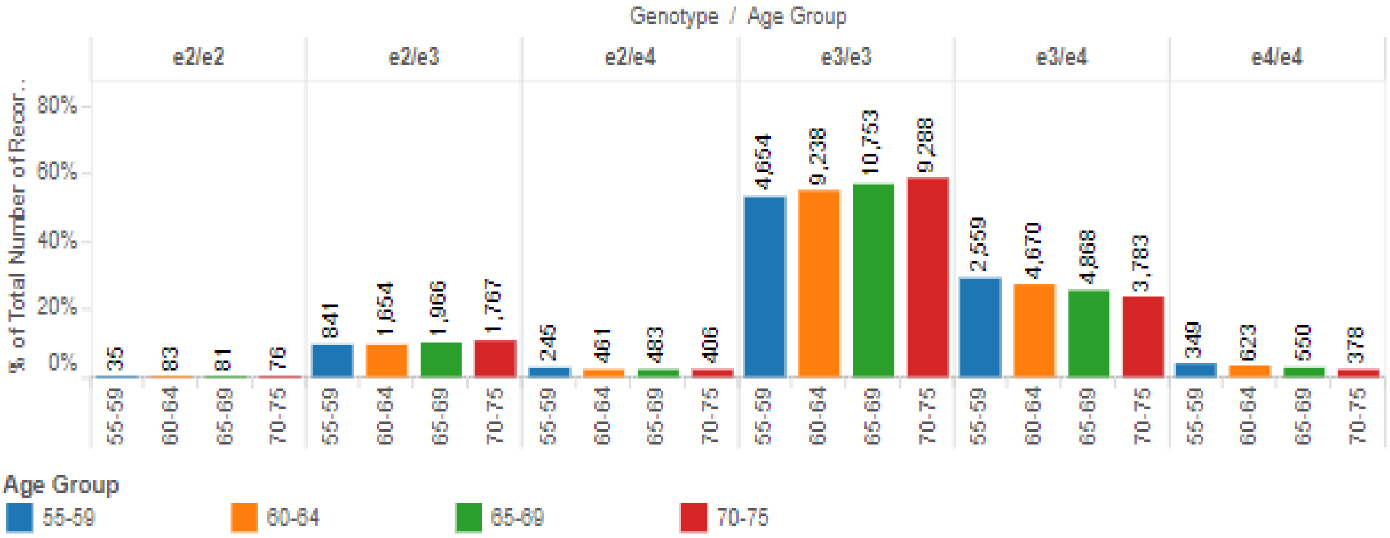
WHY NOW?

THE ALZHEIMER'S PREVENTION REGISTRY IS A PARTNERSHIP OF:

- Began with API's interest in enrolling cognitively unimpaired APOE4 homozygotes in a prevention trial
- Currently helping to recruit for 39 studies, primarily in US
- Offers several email subscriptions services: monthly newsletter, community events, study opportunities
- ~86,000 adults age 60+ receive our emails
- highly engaged, average 30-40% email open rates
- not representative of US population, predominately white women (focus of pending R01 grant)

Recruitment Registry Example: GeneMatch

- GeneMatch has enrolled >90,000 cognitively healthy 55-75 year olds in the US
- CLIA-certified APOE genotypes in >62,000



- GeneMatch as a US recruitment resource for the API Generation Program

# of Referrals to Generation	# of participants who have opened the invitation	# of participants who have accepted the invitation	# of participants who have declined the invitation	Referrals contacted by site
14,455	9,771	4,705	246	4,299

Langbaum et al, *Alzheimer's & Dementia* (in press)

API Colombia Registry

- Led by Francisco Lopera & his Grupo Neurosciences de Antioquia (GNA) in partnership with API
- Includes more than >5,800 persons, 8-75 years of age, from the largest ADAD kindred, including ~1200 *PSEN1 E280A* mutation carriers--& 6 homozygotes
  - e.g., plasma NfL study in more than 1,100 carriers & 1,100 age & sex-matched non-carriers.
- Blood samples & genetic testing in all; clinical & cognitive assessments in most
- Sole recruitment mechanism for the API ADAD Colombia Trial
- Supports observational, genetic, brain imaging, fluid biomarker & neuropathological studies
- Potential to extend to other autosomal dominant AD & CADASIL kindreds
- Foundation for other observational, biomarker, treatment & prevention studies

Rios-Romenets et al, *J Prev Alzheimers Dis* 2018

Future Direction: Amyloid Blood Test Screening Program

- Building off the GeneMatch model, we have been exploring the development of an Aβ blood test screening program
  - To accelerate & improve the efficiency of enrolling Aβ+ participants (including APOE4 non-carriers) in prevention trials
  - To provide a resource of blood samples & brain imaging data for the further evaluation of different Aβ tests (including a subset of persons who with a negative blood test)
  - To provide a foundation for the potential use of Aβ blood tests as a screening tool in the clinical setting

Challenges to the development of recruitment registries – The tip of the iceberg!

- Even if you build it, they may not come! Requires considerable advertising & outreach to enroll participants
    - Attracting healthy people
    - Limited diversity. Most respondents are white, educated & female (though some can be gait-keepers for other eligible participants)
- One size does not fit all: best practices are limited in terms of their generalizability
    - How much data do you collect at signup? Different thresholds of commitment at entry yield different populations & results
- Requires a high level of customer service & continued engagement with enrollees
    - To date, most registries are only in English
- Navigating a complicated regulatory / legal landscape to…
    - Collect personally identifiable information (PII) & protected health information (PHI)
    - Connect people to studies & provide metrics of study enrollment success
    - Collect DNA & perform genetic tests
- Funding
    - NIH does not support "infrastructure" for registries, but supports cohort studies
- Creating the IT infrastructure is time consuming & expensive
    - No "out of the box" solution
- Website design matters

Future Directions

- Gain a deeper understanding of motivators & barriers
  - particularly for under-represented racial, ethnic & male groups
- Monitor & continue to optimize our registries' performance & impact
  - including their impact on study engagement, enrollment, & retention
- Partner with Ethics Committees / IRBs:
  - work towards using more motivational, inspirational language to encourage enrollment, particularly for healthy adults & under-represented groups
  - find seamless mechanisms to share participant PII/PHI
- Incorporate new features & technologies to online registries to promote engagement, retention & data collection
  - e.g., text messaging, wearable technologies, etc
- Translate registries to other languages
  - Would require multilingual staff for registries, study sites
  - Not just the websites, but also all retention/engagement emails, etc
- Work with & support other registries
- Challenge: How to extend to other countries
  - For instance, how to address European Union Global Data Protection Requirements (GDPR) & other regulatory & language requirements

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