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Demographics of Survey Respondents

- Autosomal dominant Alzheimer's disease (ADAD), caused by pathogenic variants in *APP*, *PSEN1*, or *PSEN2*, is a rare, highly penetrant form of AD with predictable midlife onset¹.
- First-degree relatives of mutation carriers face a 50% probability of inheritance, and biological changes begin more than 15 years before symptom onset².
- Recent FDA approvals of anti-amyloid therapies have introduced new ethical and regulatory questions around trial design, genetic disclosure, and risk tolerance³.
- Despite advances in biomarker discovery and prevention trials, the lived experiences and treatment priorities of ADAD families remain underrepresented in therapeutic development and regulatory decision-making.
- To address this gap, Youngtimers — a nonprofit dedicated to improving the lives of individuals and families impacted by ADAD — organized a US FDA Patient Listening Session on December 10, 2025.
- Here, we analyze perspectives from that session to identify community priorities and unmet needs relevant to ADAD drug development and clinical trial design.

Methods

- Qualitative: Personal testimonials from nine ADAD patient and caregiver advocates delivered during an FDA Patient Listening Session organized by Youngtimers on December 10, 2025; analyzed using reflexive thematic analysis (RTA).⁴
- Quantitative: Electronic survey - developed in partnership with Youngtimers, biostatisticians, and AD clinical trialists - was distributed between November 4, 2024–January 15, 2025 via three platforms: the Youngtimers email listserv (n=417), the DIAN Expanded Registry (n=556), and a closed ADAD Facebook group (n=730). 145 of 184 responses (with available genetic status data) were included in the final analytic sample and stratified across four ADAD mutation carrier status groups.
- Ethics: Informed consent was confirmed prior to participation. All procedures were approved by WCG IRB (#2025-4113).

FDA Listening Session Participants

Nine advocates participated: six at-risk individuals or confirmed mutation carriers and three spousal caregivers. Participants represented all three ADAD-associated genes (PSEN1, PSEN2, APP), with estimated family age of onset ranging from ~40–58 years.

- **Mutation & clinical status:** 3 presymptomatic PSEN1 carriers, 1 symptomatic APP carrier, 1 presymptomatic PSEN2 carrier, 1 at-risk (status unknown)
- **Age:** Carriers/at-risk individuals: range 41–56 years (age not specified for 2 participants); spousal caregivers: not specified
- **Sex:** 3 female, 3 male (carriers/at-risk); 3 female (caregivers)
- **Ethnicity:** 1 Hispanic or Latino; 8 not Hispanic or Latino or not specified
- **Clinical trial participation:** 5 of 6 currently participating (83%) — 2 in open-label extension receiving anti-amyloid (IV); 1 in secondary prevention trial with guaranteed anti-amyloid (IV) + randomized placebo/anti-tau arm; 1 in primary prevention trial randomized to anti-amyloid or placebo (subcutaneous)
- **Interest in genetic disclosure:** 2 learned for guaranteed active treatment in an open-label extension; 2 learned independently outside a trial; 1 learned after symptom onset; 1 declined for a trial but would test for an FDA-approved therapy.

References

1. Bateman RJ, et al. *N Engl J Med*. 2012;367(9):795–804. 2. Daniels AJ, et al. *npj Dementia*. 2026;2:13. 3. Grill JD & Karlawish J. *Neurology* 2021;97(10):496–500. 4. Braun V & Clarke V. *Thematic Analysis: A Practical Guide*. SAGE Publications; 2022.

Code	Sub-theme	n	%	Frequency (N=9)
Theme 1: The burden of disease for at-risk individuals and confirmed carriers				
T1-A	Generational and familial nature of FAD	9	100%	
T1-B	Psychological toll of living at risk	8	89%	
T1-C	Mirroring — seeing one's own future in a relative's decline	6	67%	
T1-D	Fear for self, children, and future generations	9	100%	
Theme 2: The burden of disease for caregivers and families				
T2-A	Physical, emotional, and financial toll of caregiving	9	100%	
T2-B	Impact on children and family systems	7	78%	
T2-C	The long goodbye — ambiguous loss and grief	8	89%	
T2-D	Young-onset complexity	6	67%	
T2-E	Loss of function and identity: from high functioning to dependence	7	78%	
Theme 3: Genetic testing and living with genetic knowledge				
T3-A	The testing decision	5	56%	
T3-B	Receiving results	6	67%	
T3-C	Living with a positive result	3	33%	
Theme 4: Study and clinical trial participation				
T4-A	Weighing benefit against risk — the decision to participate	9	100%	
T4-B	The experience of participation — costs, rewards, and meaning	6	67%	
Theme 5: What treatment means and the call for treatment access				
T5-A	Weighing benefit against risk — the decision to access treatment	8	89%	
T5-B	The call for pre-symptomatic access for all	8	89%	

Table 1. Themes and sub-themes identified through reflexive thematic analysis (RTA) of FDA Patient Listening Session testimonials (N=9). Advocates were invited to address six FDA-suggested topic areas: symptoms, diagnosis and disease progression, treatments and disease management, considerations for possible new treatments, clinical trial preferences, and quality of life. Themes emerged organically from the testimonials within these topic areas. The final codebook comprised 5 themes and 12 sub-themes. Frequency reflects the proportion of participants whose testimony contributed to each sub-theme; percentages are not expected to sum to 100%. Bar length reflects proportional frequency colors correspond to the five overarching themes. n = number of participants; % = percentage of total participants.

Key Take-aways from Session

- **ADAD is associated with a lifelong psychological burden.** Advocates described living for decades under near-certain disease — experiencing chronic dread, anticipatory grief, and altered life planning long before symptoms appear. *"I've had this dark cloud over my head for 15 years... I don't remember what it's like to feel normal. I don't remember what it's like not to think about this every day."*
- **The disease destroys multiple generations simultaneously.** Families navigate overlapping roles as carriers, caregivers, and parents of children with a 50% inheritance risk, creating compounding emotional and financial harm across generations. *"For as long as grandma's and her ancestor's genes are alive in us, this story repeats itself generation after generation. Alzheimer's disease goes on walking with us and killing us very slowly again and again."*
- **Barriers to trial participation are real and varied.** Financial constraints, work obligations, and emotional unreadiness were identified as significant barriers — compounded by trial designs requiring genetic disclosure or placebo assignment. *"He is the primary breadwinner... it takes time to partake in drug infusions"; "Forcing the hardest decision I've ever had to make is not something I'm good at."*
- **Session advocates expressed high treatment risk tolerance.** Preserving function and identity matters far more than extending disease without improving quality of life. *"It's hard to imagine a risk greater than the risk of losing my ability to think and care for myself."*
- **Presymptomatic carriers cannot access approved therapies.** Despite near-certain disease progression, confirmed carriers cannot access anti-amyloid therapies before symptom onset, and urgently called on the FDA to expand drug labeling to include presymptomatic confirmed carriers and reconsider placebo-controlled trial designs. *"By the time I show symptoms, it will already be too late."*

Genetic Testing and Disclosure

Survey Respondents (N=145):

- **Sex:** 64% female, 35% male
- **Race/ethnicity:** 93% white (any ethnicity); 14% Hispanic/Latino (any race)
- **Education:** 69% bachelor's degree or higher
- **Age:** Mean 47.6 years (SD 13.9)
- **ADAD status:** Known carrier (n=64), at-risk untested (n=35), gene negative (n=28), not at ADAD risk (n=18)

- Among all 145 respondents, 64 were known ADAD carriers and 28 were gene negative.
- Of the remaining 35 at-risk untested individuals, 16 (45.7%) expressed interest in learning their genetic status and 19 (54.3%) preferred not to know.

**Among those preferring not to know
their genetic status at time of survey
(n=19):**

Would access to an FDA-approved treatment change your mind?

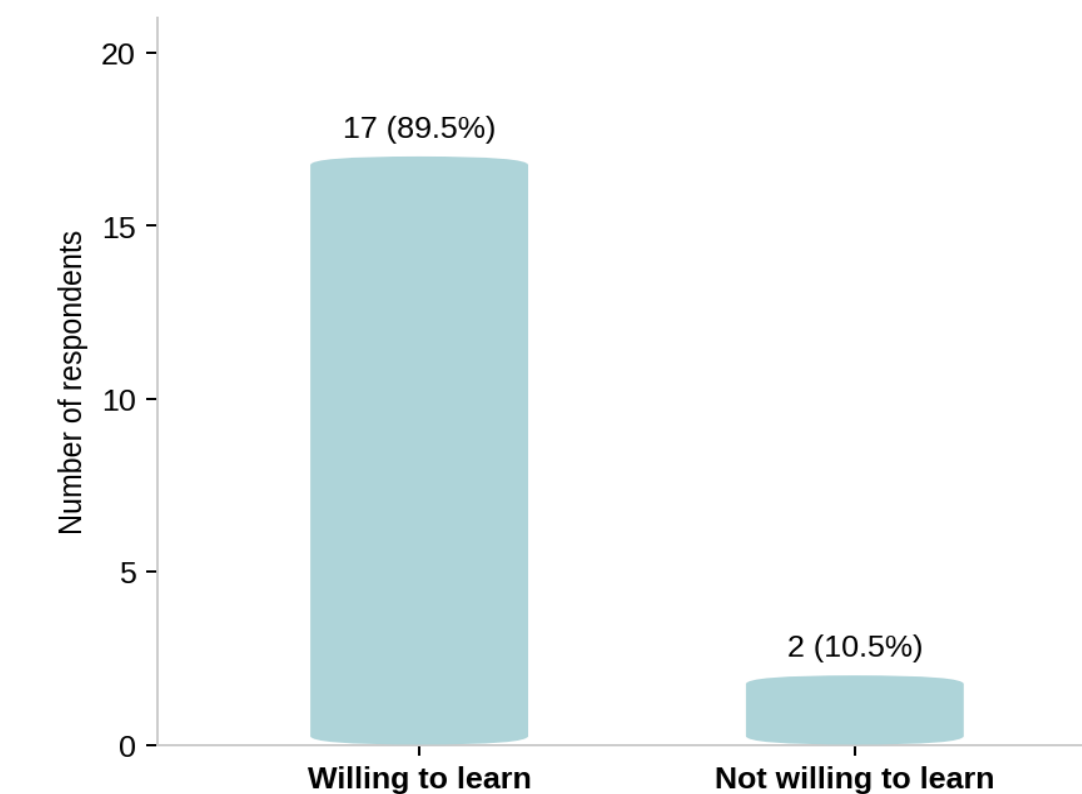


Figure 1. Among at-risk untested respondents who preferred not to know their genetic status (n=19), the majority (89.5%) would reconsider genetic testing if it facilitated access to an FDA-approved disease-modifying therapy.

Barriers to Research Participation

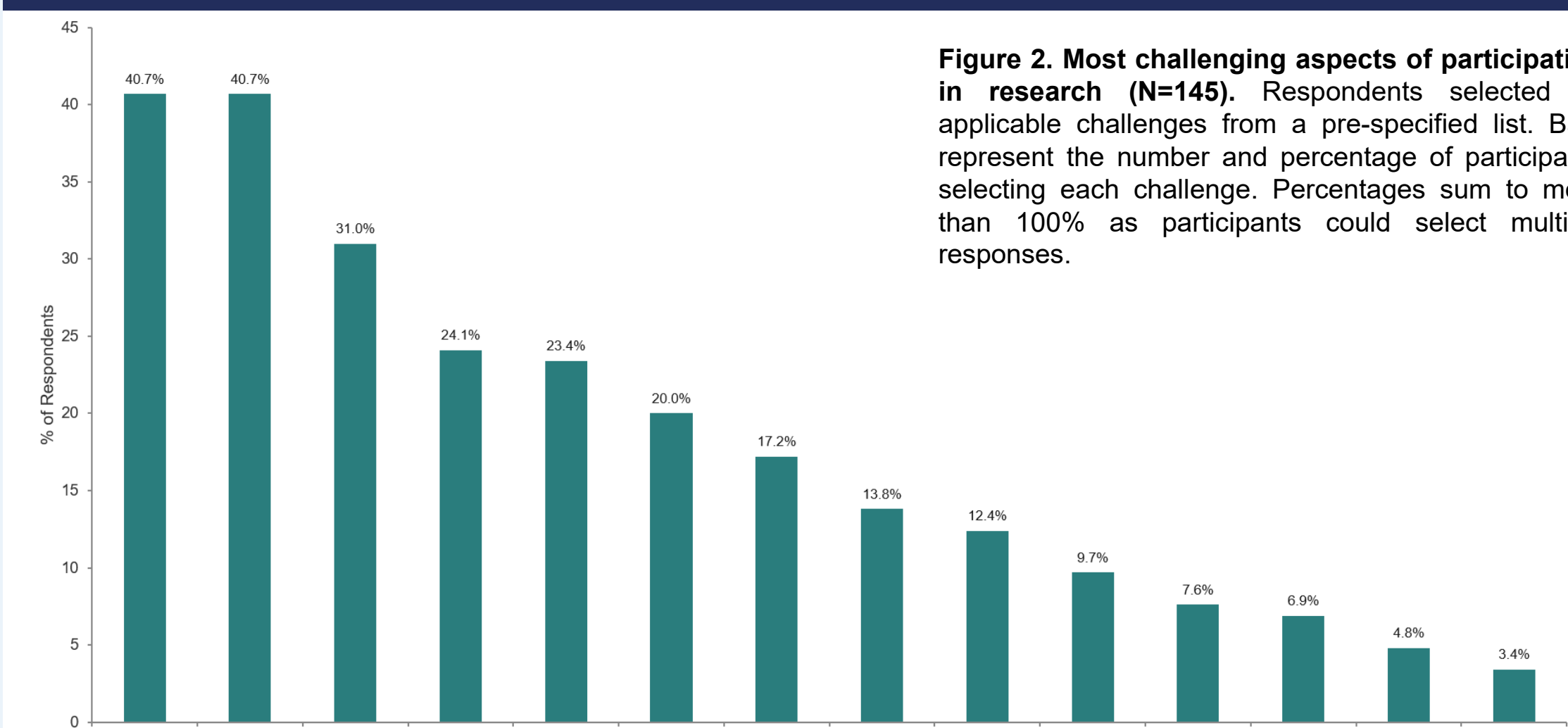


Figure 2. Most challenging aspects of participation in research (N=145). Respondents selected all applicable challenges from a pre-specified list. Bars represent the number and percentage of participants selecting each challenge. Percentages sum to more than 100% as participants could select multiple responses.

Conclusions

- **Patient perspectives reveal the profound psychological and multigenerational burden of ADAD.** Lived experiences of mutation carriers, at-risk individuals, and caregivers highlight unmet needs in trial design, treatment access, and regulatory policy that are not captured by clinical endpoints alone.
- **Integrating patient priorities can improve trial design and expand research participation.** Community perspectives highlight specific barriers — including genetic disclosure requirements and placebo assignment — that if addressed, can make trials less burdensome to participants while maintaining scientific rigor. A major patient concern remains access to approved therapies with genetic confirmation prior to symptom onset.

Acknowledgements

The utmost gratitude goes to the ADAD family members who gave their time and shared their perspectives. Their willingness to participate — is the foundation upon which meaningful scientific progress is built. We also thank the Youngtimers team for their dedication and coordination of the FDA Patient Listening Session and for their tireless commitment to elevating the patient voice in Alzheimer's disease research.