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Public perceptions related to healthcare preparedness to anti-amyloid therapies for Alzheimer's Disease in Japan

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Abstract

Background The approval of lecanemab, an anti-amyloid therapy for Alzheimer's disease (AD), necessitates addressing healthcare preparedness for disease-modifying treatment (DMT) to ensure appropriate, safe, and sustainable drug administration. Understanding public perceptions on this matter is crucial. We aimed to assess discrepancies and similarities in the perceptions of Japanese trial-ready cohort study ('J-TRC webstudy') participants and clinical specialists in the fields of dementia treatment and radiology, concerning affairs related to challenges in DMT preparedness.

Methods This was a cross-sectional prospective observational study conducted in November–December 2023. The J-TRC webstudy participants were invited to participate in an online survey using Google Forms, and clinical specialists were invited to complete a mail-based survey. Main questionnaire items had been designed to be common in both surveys, and their responses were analyzed for participant attributes, interests, attitudes, expectations, and concerns about DMTs without specifying lecanemab.

Results Responses were obtained from $n = 2{,}050$ J-TRC webstudy participants and $n = 1{,}518$ clinical specialists. Compared to specialists, more J-TRC respondents perceived the eligible proportion for DMT as smaller (59.1% versus 30.7%), perceived the eligible severity for DMT as more limited (58.0% versus 24.5%), and perceived the efficacy of DMT as slightly more encouraging (29.3% versus 34.8%). In terms of treatment prioritization, both J-TRC respondents and specialist respondents exhibited similar levels of acceptance for prioritizing patients to treat: e.g., approximately two-thirds endorsed patient prioritization under hypothetical resource constraints or other reasons. A medical rationale emerged as the most compelling reason for acceptance of patient prioritization across the surveys. In contrast, the need to address vulnerable populations was the reason that led to the least acceptance of prioritization, followed by economic considerations.

Conclusions Our findings offer valuable insights into the discrepancies in knowledge and perception between patients and healthcare providers. This could enhance the delivery of patient information in clinical settings and inform the discussion surrounding patient prioritization strategies.

Keywords Public perceptions, Online survey, Trial-ready cohort, Disease-modifying therapy, Patient prioritization

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Introduction

Alzheimer's disease (AD) is a leading cause of cognitive decline in the aged population [1]. In Japan, the number of dementia patients in 2025 is estimated as approximately 4.7 million (13% of aged population) [2], and the total annual healthcare cost required for Japanese AD dementia individuals is estimated at approximately 7 billion USD (when 1 USD = 150 JPY) [3]. Lecanemab, a disease-modifying therapy (DMT) drug for AD, has been approved for patients with early AD in the United States [4], Japan [5], and mainland China [6]. In Japan, lecanemab received full approval in September 2023, with coverage by public health insurance since December 2023 [7]. The maximum annual number of people to be treated with lecanemab in Japan has been estimated by the pharmaceutical company to be about 32,000 [8].

The clinical implementation of lecanemab has heightened awareness regarding the readiness of the healthcare system in Japan for DMT [9–11]. The lecanemab package insert in Japan, issued in September 2023, mandated physicians to verify amyloid accumulation through amyloid positron emission tomography (PET) or cerebrospinal fluid (CSF) testing and to ascertain baseline disease severity at the mild cognitive impairment (MCI) or mild dementia stage of AD [12]. In addition, Optimal Use Guideline (OUG) for lecanemab in Japan, released in December 2023 [13], stipulates a baseline Mini-Mental State Examination (MMSE) score of 22–30 and a baseline Clinical Dementia Rating Global Score (CDR-GS) of either 0.5 or 1 for treatment eligibility. Nevertheless, the scarcity of medical facilities and specialists qualified to conduct these assessments is a concern [9–11]. The lecanemab treatment protocol requires outpatient visits for biweekly, hour-long administrations. Monitoring for adverse effects, such as Amyloid-Related Imaging Abnormalities (ARIA) [14], necessitates readily available brain MRI scanning facilities, further constraining treatment accessibility.

Furthermore, these gaps in healthcare preparedness for lecanemab treatment have raised concerns about lengthy average wait times for diagnosis, testing, and treatment: an earlier study estimated the wait times to be 19 months in the US, 14 months in the UK, 11 months in Germany, and 15 months in Japan [9]. The requirement to administer lecanemab to all patients in need at the appropriate time may not always be compatible with a first-in, first-out – or a chronological waiting list approach. For example, for barely qualified individuals, such as those with a borderline MMSE score of 22, or those nearing a transition from mild to moderate dementia, treatment delays of 1 year could result in a loss of therapeutic opportunities. For non-urgent clinical services akin to DMT for AD, it has been considered that the waiting list needs to be managed in a fair manner so that patients with greater need or severity will be given priority for treatment [15, 16] and that negative sequelae from the waiting list approach would be reduced. Patient prioritization, which was defined in some earlier literature as such"*the process of ranking referrals in a certain order based on criteria*" [15, 17], may be one strategy that improves fairness of the waiting list approach, and several patient prioritization tools have actually been developed for many non-urgent health services including elective surgery [15]. However, it remains uncertain whether any form of 'prioritization' for anti-amyloid treatments is acceptable in the case of AD treatment.

Hence, the diagnosis, administration, and monitoring infrastructures encounter practical challenges in the safe, effective, sustainable, and appropriate delivery of approved DMTs beyond just lecanemab. Overcoming these hurdles necessitates a comprehensive understanding of public perceptions, including those of potential patients, regarding DMT drugs, requisite testing, and other related matters, with a focus on their knowledge, expectations, concerns, demands, and viewpoints. Such insight could pinpoint the knowledge and perception disparities between patients and healthcare providers, improving patient information delivery in clinical settings. It could also inform discussions about prioritization of treatment.

This study aims to carry out an anonymous online survey about perceptions of DMT drugs and associated topics among participants of the Japanese trial-ready cohort study ('J-TRC webstudy') [18, 19], and comparatively analyze the responses to shared questions with those obtained from surveys of medical clinical specialists. While the opinions of the questionnaire respondents may not fully represent the broader Japanese population, this study will offer valuable insights into the perspectives of individuals with a vested interest in dementia research and future DMT treatments.

Methods

Survey to J-TRC webstudy participants

The J-TRC webstudy is an online registry designed to enroll preclinical AD subjects for preventative trial facilitation [20]. The details of the J-TRC webstudy have been described in our previous reports [18, 19]. Briefly, the J-TRC study for preclinical and prodromal AD was launched in Japan in 2019 under a research license agreement with the Alzheimer's Therapeutic Research Institute. It has two main study components: the J-TRC webstudy and J-TRC onsite study. The J-TRC webstudy (https://www.j-trc.org/), which is designed based on the APT Webstudy (https://www.aptwebstudy.org/) for Japanese cognitively normal elderly volunteer participants

aged 50–85 years, is monitored by web-based remote assessment of the cognitive function instrument (CFI) [21] and CogState [22] every 3 months. The J-TRC website is accessible only domestically within Japan. Within approximately 4 years since its launch, the J-TRC web study has recruited more than 10,000 eligible online participants from all over Japan. Individuals with an increased risk of elevated brain amyloid or cognitive decline are referred to the J-TRC onsite study for detailed in-person cognitive assessments, *APOE* genotyping, blood biomarker testing (e.g., plasma Aβ and p-tau), and determination of brain amyloid status by amyloid PET. The J-TRC onsite study, which is designed based on the TRC-PAD in-person study in the United States, aims to build a large (n > 300) cohort of Japanese individuals with preclinical AD.

The procedure of our online survey is largely in accordance with our previous online survey conducted in June 2023 in terms of J-TRC website usability [23]. On September 25, 2023, we extracted the data of J-TRC webstudy participants eligible for this survey: those who had completed registration to the J-TRC website, given consent to participate in the study, and completed one or more CFI tests. Among them, 10,414 web study participants with valid e-mail addresses were included as eligible users to be sent an invitation e-mail containing the web address of the online questionnaire. E-mails were sent in the morning (6:00 am–7:00 am), only once per participant during the period between November 28 and December 2, 2023. The timing of this survey corresponds to the interval period between the full approval of lecanemab in Japan in September 2023 and the publication of the Optimal Clinical Use Guideline (OUG) of lecanemab in Japan on December 19, 2023. This means that at the time of the survey, questionnaire respondents had little idea about what kind of regulations might actually be in place for eligible patients and treatment facilities. No incentives (e.g., monetary gifts or lotteries) were provided to the questionnaire respondents. We have not sent thank-you mass e-mails with reminders.

An online questionnaire was administered using Google Forms provided in the Japanese language (https://www.google.com), without requiring personally identifiable information (e.g., name, account ID, e-mail address, or date of birth). It can be accessed via PCs, tablets, or smartphones. We used an anonymous method for collecting responses: we did not require respondents to log into their Google accounts to answer the Google Form questionnaire, nor did we require them to fill in their J-TRC webstudy accounts. This is because we wanted to gain as many responses as possible, even at the expense of respondents' traceability. Consequently, we were unable to exclude potential duplicate responses from the same individual. However, to reduce double responses, we included a caution statement "Please respond to the questionnaire only once." within the invitation e-mail.

Dropout analysis of the survey has been conducted and reported elsewhere [24], revealing significantly higher response rates among women (e.g., relative risk (RR) of response approximately 1.2 compared to men), lower response rates among non-retired individuals (RR approximately 0.8 compared to retired individuals), and lower response rates among younger individuals compared to older individuals.

Survey to specialist clinicians

Prior to our current online survey, with the cooperation of relevant academic societies, we had designed some of the questions in our survey in collaboration with other paper-based surveys on similar issues (i.e., perceptions of DMT treatment) that had been conducted in October and November 2023 with medical specialist clinicians in the field of dementia treatment or radiology. These surveys were led by one of our authors (T.A) and his colleagues as a special research project supported by the Ministry of Health, Labour, and Welfare. The cooperative design of questions was intended so that our results can be comparatively analyzed with the results obtained from specialists. Specialists certified by the Japan Society for Dementia Research (https://square.umin.ac.jp/dementia/) or the Japanese Psychogeriatric Society (http://www.rounen.org) were asked to answer the survey for specialists in dementia treatment, and specialists certified by the Japanese Society of Nuclear Medicine (https://jsnm.org) or members of The Japanese Society of Neuroradiology (https://neurorad.jp) were asked to answer the survey for specialists in radiology.

The commonly-designed questions are shown in Table 1: self-evaluated knowledge about DMT (Q17), willingness to receive DMT treatment (Q18), impressions about the range of DMT eligibility (Q19, Q20), impression about the efficacy of DMT (Q21), impressions about blood based biomarkers (e.g., plasma Aβ) (Q28), and perceptions about prioritizing treatment (Q41-Q45).

The survey of dementia treatment specialists gathered n = 1,157 eligible responses, and the survey of radiology specialists had gathered n = 361 eligible responses. We obtained result data of answers to the commonly-designed questions, and used them for comparative analysis with our survey results. Dropout analysis of the surveys of specialists was not conducted because we have not obtained individual specialists' personal background information (e.g., age and sex).

Table 1 Commonly designed questionnaire contents across surveys to J-TRC users and specialists

Question No	Questions (in italic) and answer choices
Q17 Knowledge about anti-amyloid drugs	*How much do you know about this anti-amyloid drug so far?* *Please select the choice from 1 to 5 that best applies.* (*) Likert scale [1–5]: 1 = I am not familiar with it at all. ~ 5 = I am very familiar with it
Q18 Willing to undergo anti-amyloid drugs	*If anti-amyloid medications were to become available in Japan with reimbursement, and you were in a medical condition that might require such treatment, would you be willing to undergo it?* *Please select the choice from 1 to 5 that best reflects your current stance.* (*) Likert scale [1–5]: 1 = I would not want to undergo at all. ~ 5 = I would be very willing to undergo
Q19 Impression about eligible proportion	*Not everyone who wishes to be treated with anti-amyloid drugs is eligible for the treatment, as there are several criteria for use, including the presence of amyloid accumulation in the brain. For instance, in some previous clinical trials, it was estimated that only about 20–40% of those who wanted to participate were actually eligible for the treatment.Please select the choice from 1 to 5 that best describes your impression about this proportion of treatment eligibility.* (*) Likert scale [1–5]: 1 = Very few ~ 5 = Very many
Q20 Impression about eligible disease severity	*Additionally, anti-amyloid therapy may not be suitable for individuals with advanced dementia. In some earlier clinical trials, eligibility was limited to those in the pre-dementia stage (mild cognitive impairment: MCI) or with mild Alzheimer's disease (AD) dementia. Please select the choice from 1 to 5 that best describes your opinion about the scope of eligibility for treatment, specifically for 'MCI and mild AD.* (*) Likert scale [1–5]: 1 = Very narrow ~ 5 = Very broad
Q21 Impression about drug efficacy	*Anti-amyloid drugs do not guarantee 100% prevention of the onset of dementia or a complete halt in its progression. In previous trials, the drugs were reported to 'slow the rate of cognitive decline by about 20–30% (compared to untreated individuals)' and 'delay progression to a more severe stage by an average of 2–3 years'. Please select the choice from 1 to 5 that best describes your opinion regarding the efficacy of these drugs* Likert scale [1–5]: 1 = Seems completely ineffective ~ 5 = Seems highly effective
Q28 Expected roles of blood-based biomarkers	*Please select all of the following choices that apply to what expectations you feel about the blood tests. (Multiple selections allowed)* ✓ Alzheimer's disease can be diagnosed by blood testing ✓ Alternative to amyloid PET scan ✓Alternative to cerebrospinal fluid testing ✓ We can know in advance if we need an amyloid PET scan or cerebrospinal fluid test ✓ I am not sure. / Others
Q41 Pros/cons of prioritization in general terms	*It may not be possible to provide treatment to everyone who need it for various reasons such as insufficient preparedness of healthcare systems or financial issues. What do you think about prioritizing or limiting the treatment based on certain criterion? Please select the one that best fits your view* a) Even if treatment cannot be provided to all patients who need it, prioritizing of treatment should not be conducted b) If treatment cannot be provided to all patients who need it, it is acceptable to prioritize doctors and medical institutions to some extent, such as by imposing conditions on them c) If treatment cannot be provided to all patients who need it, it is acceptable to prioritize patients to some extent, for example, such as by imposing conditions on them d) If treatment cannot be provided to all patients who need it, it is acceptable to prioritize both doctors/medical institutions and the patient to some extent e) I am not sure. / Others
Q42 Pros/cons of prioritization focusing on medical rationale	*When it may not be possible to provide the treatment to everyone who need it, what are your thoughts on prioritizing or limiting the treatment,* ***especially in terms of aspects of medical rationale (e.g., therapeutic efficacy, frequency of adverse drug reactions,*** **etc.)***? Please select the one that best fits your view* • Same answer choices as of Q41 (a) ~ (e)

Table 1 (continued)

Question No	Questions (in italic) and answer choices
Q43 Pros/cons of prioritization focusing on economical aspects	*When it may not be possible to provide the treatment to everyone who need it, what are your thoughts on prioritizing or limiting the treatment,* ***especially from health economic aspects (i.e., national financial perspective, whether the benefits are worth the cost,*** **etc.)?** *Please select the one that best fits your view* • Same answer choices as of Q41 (a) ~ (e)
Q44 Pros/cons of prioritization focusing on impact on patients' lives	*When it may not be possible to provide the treatment to everyone who need it, what are your thoughts on prioritizing or limiting the treatment,* ***especially in terms of their impact on people's lives (e.g., people who live alone or have young dementia may be likely to benefit more from maintaining their life functions by drugs)?*** *Please select the one that best fits your view* • Same answer choices as of Q41 (a) ~ (e)
Q45 Pros/cons of prioritization focusing on addressing vulnerable people	*When it may not be possible to provide the treatment to everyone who need it, what are your thoughts on prioritizing or limiting the treatment,* ***especially in terms of addressing socially vulnerable groups (e.g., those with little support in their lives, economically impoverished,*** **etc.)?** *Please select the one that best fits your view* • Same answer choices as of Q41 (a) ~ (e)

Questions with asterisks (*) are mandatory to answer

MCI Mild cognitive impairment, *AD* Alzheimer's disease

Questionnaire

The questionnaire was made up of 55 questions in total following the background explanations for each topic, over 19 pages written in Japanese, requiring approximately 30–40 min to complete. The English-translated version of questionnaire explanations, questions, and answer choices are provided in Additional file 1. Questions are composed of those about the respondents' attributes (Q1-Q16, Q33, Q55), and those about the respondents' perceptions of DMT drugs or related affairs (Q17-Q32, Q34-Q54). Among these 55 questions, 22 are mandatory to answer. The majority of the questions required the selection of only one answer choice that best applied, but for some questions respondents were asked to select multiple answers that applied.

Questions Q41-Q45 are about prioritizing treatment. The question Q41 is "*As mentioned above, it may not be possible to provide treatment to everyone who need it for various reasons such as insufficient preparedness of healthcare systems or financial issues. What do you think about prioritizing or limiting the treatment based on certain criteria?*", and the questions Q42-Q45 are modified versions of Q41 from specific points of view. The question Q41 asks about the pros and cons in general terms for prioritizing DMT treatment by service providers (i.e., medical facilities or doctors) or by patients. This question assumes a hypothetical case of practical shortcomings in the preparedness for DMT treatment, asking whether it is acceptable to prioritize service providers (i.e., facilities and doctors) who should administer DMT treatment ("acceptable for prioritization of facilities"), and whether it is acceptable to prioritize patients who should receive DMT treatment ("acceptable for prioritization of patients"). Prior to this question, detailed explanations about the background circumstances as to why resource shortcomings in DMT treatment may occur are shown in the questionnaire page.

The modified questions Q42-Q45 focus on specific point of view (unlike *in general terms* in Q41) in considering the pros and cons of prioritization: medical rationale (Q42), health economic perspectives (Q43), impact on patients' lives (Q44), and addressing socially vulnerable people (Q45). These questions do not include specific examples of the assumed settings, and they simply ask respondents' impressions of pros/cons of prioritization in terms of these points of view. In general, it has been widely observed in clinical practice to limit eligible patients or facilities for some specialized treatments based on the safety and efficacy of the treatments, such as in the form of practice guidelines. This is also true in the case of lecanemab treatment, since AUR [4] and OUG [13] for lecanemab require that eligible patients have an MMSE score of 22 or more and a CDR-GS score of 0.5 or 1 at baseline. Such criteria exclude non-eligible patients from the ranking of referrals for treatment, which means that "patient prioritization from medical rationale" (Q42) has been in some ways accepted to varying degrees. Thus, we set Q42 as a reference to measure the degree of acceptance toward prioritization in other similar questions (Q43-45).

Statistical analysis

Data acquisition period was determined as four weeks from the day of invitation e-mail sending. All data preprocessing and analyses were conducted using R software. First, answers to questions for J-TRC webstudy

participants are summarized: numerical variables and Likert scale answers are summarized using median and interquartile range (IQR), and categorical variables are summarized using frequency and proportion (%).

Second, we analyzed Likert scale results (scales: 1–5) on the impression about DMT drugs (Q17-Q21) for integrated data comprised of J-TRC participant survey and specialist surveys. For each scale score in Q17-Q21, we conducted linear regression analysis using the following equation:

- Model (A):$Likertscale = \beta_0 + Data \cdot \beta_1$

where β_0 is the intercept and *Data* is the survey group of participants (i.e., J-TRC webstudy participants, specialists in dementia treatment, and specialists in radiology). In this model, β_1 is the coefficient we want to obtain in order to understand the difference in the responses among the examined data groups.

Third, we analyzed perceptions regarding the prioritization of treatment (Q42-Q45), using data from the J-TRC participant survey and specialist surveys. Responses to Q42-Q45 were bifurcated into a binary variable indicating acceptance towards prioritizing patients receiving DMT treatment (e.g., choices [c] and [d] for "yes", and choices [a] and [b] for "no" towards it), or acceptance towards prioritizing facilities administering DMT treatment (e.g., choices [b] and [d] for "yes", and choices [a] and [c] for "no" towards it). These question answers to Q42-Q45 were collapsed into a single variable that represents a set of (four) repeated measures for each survey respondent, and we conducted mixed logistic regression analysis on the target binary variable (i.e., "acceptance towards prioritization of patients (or facilities)") based on the following equations, which allowed us to account for within-participants variability:

- Model (B-1): $log\left(Odds_{patients,Data}\right) = \beta_0 + Focus \cdot \beta_1 + RespondentID \cdot \gamma_0$
- Model (B-2): $log\left(Odds_{patients,Data}\right) = \beta_0 + Focus \cdot \beta_1 + Age \cdot \beta_2 + Sex \cdot \beta_3 + Education \cdot \beta_4 + Living \cdot \beta_5 + Retired \cdot \beta_6 + Family \cdot \beta_7 + RespondentID \cdot \gamma_0$
- Model (C): $log\left(Odds_{facility,Data}\right) = \beta_0 + Focus \cdot \beta_1 + RespondentID \cdot \gamma_0$

In the equations above, Data is the survey group of participants (i.e., J-TRC participants, specialists in dementia treatment, and specialists in radiology). The target variable in the above models is the acceptance towards prioritizing patients (yes/no, in model [B]) or facilities (yes/no, in model [C]). β_0 represents the fixed intercept, Focus is a categorical variable on the specified point of focus (i.e., Q43-Q45) with the Q42 response as a reference, and γ_0 denotes a random intercept by the respondent [25]. Model (B-2) was only applied to J-TRC participant data. The variable *Age* represents the respondent's age in decades, Sex denotes whether the respondent is female, *Education* indicates additional education years after graduating from high school (e.g., 0 indicates graduation from high school), *Living* refers to the respondent's living arrangement (i.e., living alone or not), *Retired* denotes whether the respondent is currently retired or not, and *Family* means whether the respondent has any family history of dementia or AD. β_1 is the coefficient we want to obtain. The obtained $exp(\beta)$ corresponds to the adjusted odds ratio (OR). When the lower 95% confidence interval (CI) of OR is higher than 1, it is considered significantly high. The mixed logistic regression was performed using R package {*lme4*} [26]. Some questions, including Q41-Q45, were not mandatory to answer, leading to missing values in the analysis: for the analysis with models (B) and (C), a listwise method was used to deal with the missing values.

Ethics

The J-TRC webstudy was approved by the University of Tokyo Graduate School of Medicine Institutional Ethics Committee (ID:2019132NI-(3)), and online informed consent was obtained from individual participants upon registration. The online survey was also approved by the local ethics committee.

Results

Overview

Within four weeks (28 days) of the response acceptance period after sending the invitation e-mail, 2,050 eligible responses were obtained. This represents 19.7% of the 10,414 J-TRC web study participants to whom we sent invitation e-mails. Respondent characteristics are summarized in Table 2: their median age is in the 60's (IQR: 50 's ~ 70's) (Q2), education history is a median of 16 years (IQR: 14 ~ 16) (Q5), and co-payment rate is a median of 30% (IQR: 20 ~ 30) (Q9). The majority of them live in the Kanto region including Tokyo (58.9%) (Q4), live with other people (83.7%) (Q6), and have a full-time or part-time job (54.5%) (Q7). Approximately half of the respondents have a parental history of AD or dementia (47.1%) (Q8). Most of them (approximately 96–99%) have never been diagnosed with AD or dementia, MCI, or preclinical AD (Q11-Q13), and have not been certified for long-term care services (98.9%) (Q16). Approximately two thirds of the respondents (66.6%) felt subjective memory decline compared to one year ago (Q14).

Table 2 Respondent characteristics of the survey to J-TRC webstudy participants

Question No	Question (abbreviated)	Summary statistics
Q1	Confirmation of respondent: Yes (vs No)	2036 /2050 (99.3%)
Q2	Age (in decades)	Median 60's (IQR: 50's ~ 70's)
Q3	Gender: Female (vs Male)	1082 /2047 (52.86%)
Q4	Region of residence: Kanto (vs others)	1207 /2050 (58.88%)
Q5	Education history: Converted to years	Median 16 (IQR: 14 ~ 16)
Q6	Living with others: Yes (vs No)	1708 /2041 (83.7%)
Q7	Current employment	Full-time job: 616 (30.05%), Part-time job: 502 (24.49%), No job: 838 (40.88%), Others: 94 (4.59%)
Q8	Family history of dementia	Parents: 966 (47.12%), Siblings: 62 (3.02%), Grandparents / ants / uncles: 266 (12.98%), Others: 128 (6.24%), None: 770 (37.56%)
Q9	Co-payment % in health insurance	Median 30 (IQR: 20 ~ 30)
Q10	Having regular visits to hospital: Yes (vs No)	1543 /2050 (75.27%)
Q11	History of dementia diagnosis: No (vs Yes)	2020 /2041 (98.97%)
Q12	History of MCI diagnosis: No (vs Yes)	2005 /2034 (98.57%)
Q13	History of preclinical AD diagnosis: No (vs Yes)	1934 /2005 (96.46%)
Q14	Subjective memory decline compared to 1 year ago: No (vs Yes)	1208 /1813 (66.63%)
Q15	Self-esimated likelihood developing dementia	Highly likely: 71 (3.46%), Moderately likely: 414 (20.2%), Slight likely: 1053 (51.4%), Already diagnosed: 12 (0.59%), Others: 500 (24.4%)
Q16	Long-term care certification: No (vs Yes)	2022 /2044 (98.92%)
Q33	Primary transportation for visiting hospital	Public (bus, train, taxi): 1172 (57.15%), Private vehicle (by others): 61 (2.98%), Private vehicle (by self): 739 (36.05%), Others: 78 (3.805%)

IQR Interquartile range, *MCI* Mild cognitive impairment, *AD* Alzheimer's disease

Respondent characteristics of medical specialists in dementia treatment (n = 1,157) and radiology (n = 361), are summarized in Additional file 2. Briefly, approximately half of specialists in dementia treatment and approximately 80% of specialists in radiology are affiliated with acute-phase hospitals where lecanemab treatment can be provided primarily (questions D1 and R1). Additionally, approximately half (47.9%) of specialists in dementia treatment have 10 years or longer of clinical experience as certified specialists (question D6), while most (78.9%) of specialists in radiology have a similar length of experience (question R7).

In all three surveys, the proportion of missing value responses to the non-mandatory questions was very low, with the highest rate being approximately 2%.

Questionnaire results (1): shared questions

A summary of shared questions (Q17-Q21, Q28, Q41-Q45) is shown in Additional file 3 for all three survey datasets. Histograms of Likert scale scores for Q17-Q21 are shown in Fig. 1. Compared to specialists in dementia treatment, J-TRC webstudy participants had less subjective knowledge about DMT (Q17) (coefficient -1.014, $p < 0.001$ in Model [A]). Meanwhile, J-TRC participants showed a more disappointing impression of the eligibility of DMT drugs than specialists in dementia treatment (coefficient -0.660 for eligible proportion (Q19) and -0.657 for eligible severity (Q20), both $p < 0.001$ in Model [A]), while specialists in radiology had no difference in their impression of DMT eligibility compared to the specialists in dementia treatment. In terms of the degree of efficacy (Q21), J-TRC participants had a slightly more positive impression than specialists in dementia treatment (coefficient + 0.1, $p = 0.004$ in Model [A]).

In terms of the expected roles of blood-based biomarkers (e.g., plasma Aβ or p-tau) (Q28), tests in the diagnosis of AD, or prescreening prior to amyloid PET or CSF tests were the top two roles expected both by the J-TRC study participants (71.0% and 56.9%) as well as the specialists in dementia treatment (43.6% and 51.6%).

Preference for prioritization (Fig. 2) showed largely similar results for both in J-TRC participants and

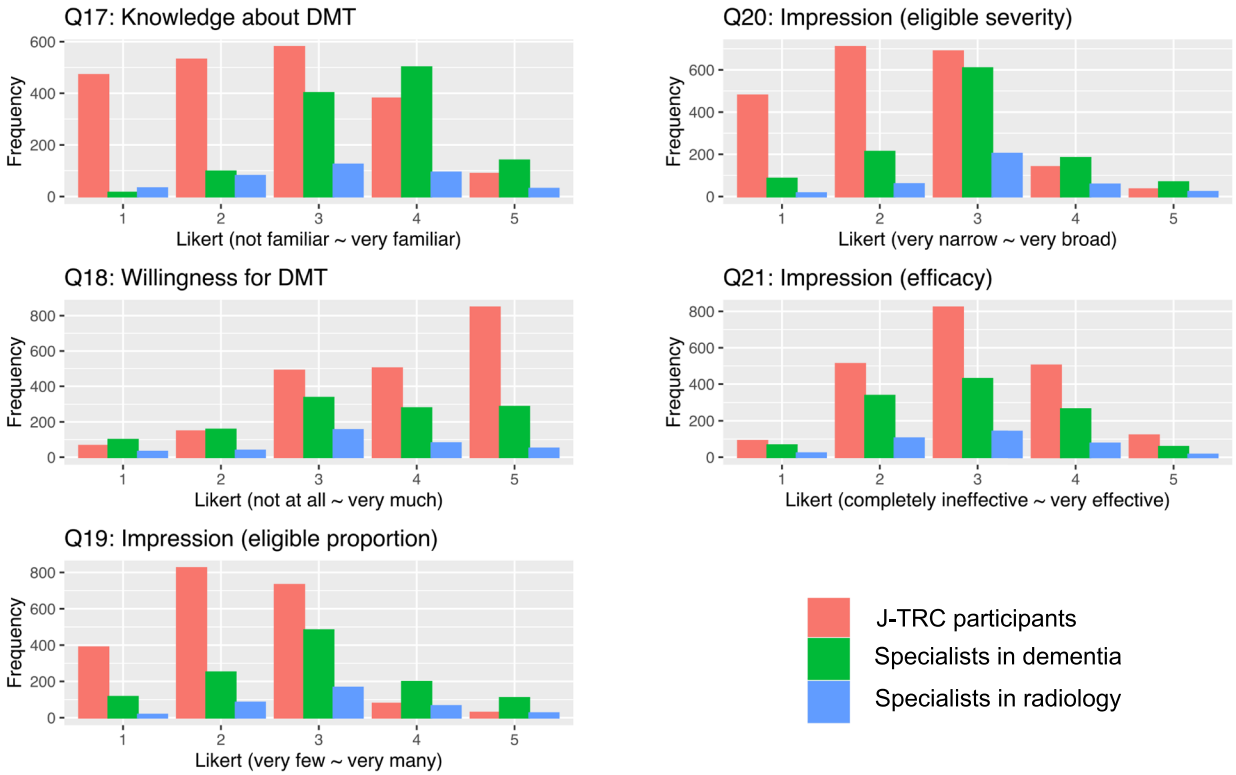

Fig. 1 Histograms of Likert scale for the perception about DMT (Q17-Q21). Compared to specialists in dementia treatment, J-TRC webstudy participants had less subjective knowledge about DMT (Q17). Meanwhile, J-TRC participants showed a more disappointing impression of the eligibility of DMT drugs than specialists in dementia treatment (Q19, Q20), while specialists in radiology had no difference in their impression of DMT eligibility compared to the specialists in dementia treatment. In terms of the degree of efficacy (Q21), J-TRC participants had a slightly positive impression than specialists in dementia treatment. These results are also summarized in Additional file 3

specialists. For prioritization in general terms (Q41), allowing prioritizing both facilities and patients was the most prevalent choice selected by J-TRC participants, specialists in dementia treatment, and specialists in radiology (38.1%, 61.1%, and 57.7%, respectively). Preference for prioritization of facilities ([b] & [d]) was expressed by 52.4% of J-TRC respondents, 85.7% of dementia treatment specialists, and 76.2% of radiology specialists. Meanwhile, preference for prioritization of patients ([c] & [d]) was expressed by 65.9% of J-TRC respondents, 67.6% of dementia treatment specialists, and 63.6% of radiology specialists.

The likelihood of accepting prioritizing patients or facilities when focusing on specific points of view to consider pros/cons of prioritization (Q42-Q45) was then analyzed by mixed logistic regression analysis (models [B] & [C]) within each survey (Fig. 3). Compared to a medical rationale, economic aspects (Fig. 3A, approximately 0.4–0.5 of OR) and addressing vulnerable individuals (Fig. 3A, approximately 0.2 of OR) were consistently less likely to be the preferred rationale for prioritizing patients. Meanwhile, the impact on patients' lives showed inconsistent likelihood of acceptance compared to that due to medical rationale (e.g., increased OR in J-TRC participants but decreased OR in specialist surveys). The preferences for prioritization of J-TRC webstudy participants remained largely unchanged even when adjusted for background features (Fig. 3A, plot A-2 versus plot A-1). In the analysis, education years was the only background variable associated with the increased preference for prioritizing patients (OR = 1.246 [95%CI: 1.105 ~ 1.406] for each additional year of education from 12 years).

Meanwhile, compared to the preference for prioritization in terms of medical rationale, addressing vulnerable people or the impact on patients' lives showed significantly lower likelihood of acceptance for prioritizing facilities (Fig. 3B) across the examined surveys consistently, while the economic aspects did not show significant increase or decrease in OR as a focus for accepting facility prioritization (i.e., 95%CI overlapping with an OR of 1).

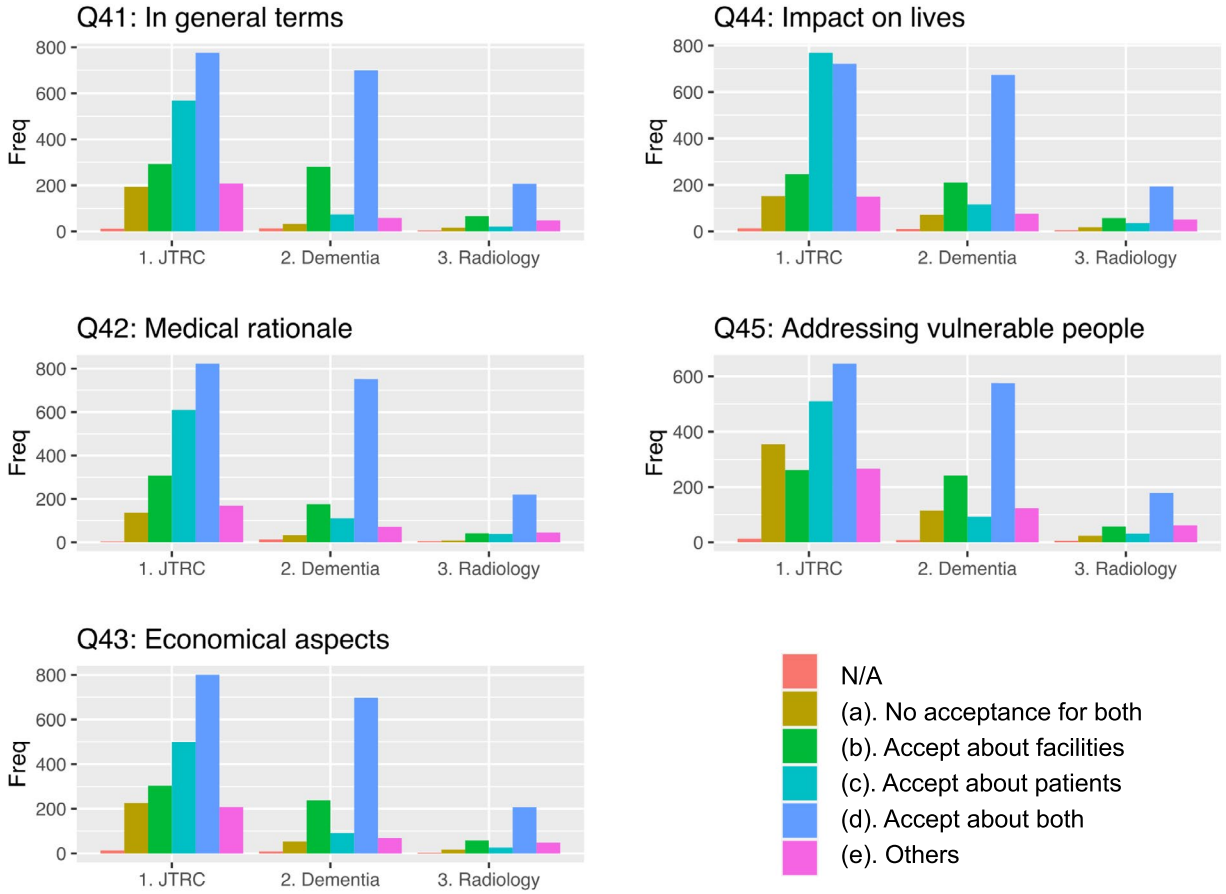

Fig. 2 Distribution of perception about patient and facility prioritization (Q41-Q45). Acceptance towards prioritization showed largely similar results both in J-TRC participants and specialists. For prioritization in a general term (Q41), allowing prioritizing both facilities and patients was the most prevalent choice selected either by J-TRC participants, specialists in dementia treatment, and specialists in radiology. Acceptance towards prioritization of facilities ([b] & [d]) was expressed by 52.4% of J-TRC respondents, 85.7% of dementia treatment specialists, and 76.2% of radiology specialists. Meanwhile, acceptance towards prioritization of patients ([c] & [d]) was expressed by 65.9% of J-TRC respondents, 67.6% of dementia treatment specialists, and 63.6% of radiology specialists

Questionnaire results (2): other questions

A summary of the remaining other questions is shown in Additional file 4. Briefly, J-TRC participants were largely willing to undergo amyloid PET (Q23) and not familiar with CSF tests (Q24). The majority of them (56.2%) were familiar with PET and CSF at a similar level (i.e., equal in Likert scale: Q22 vs Q24). Half (50.0%) of them preferred PET over CSF (i.e., larger in Likert scale: Q23 vs Q25), while few preferred CSF over PET (2.3%). They preferred PET or CSF tests to be conducted at facilities in their local area (Q26, 68.0%). Their attitudes toward blood-based biomarkers (Q27) were mainly cautious (52.4%), followed by proactive (44.7%).

Most of them (90.4%) were willing to undergo an *APOE* test (Q29), given it is a requisite of treatment ([b] and [d]: 44.6%) or it is covered by health insurance ([c] and [d]: 45.9%). Most of those who wanted to receive an *APOE* test also wanted to know the results themselves (94.5%) even if they turned out to be unfavorable ones (Q30). Genetic counseling was also desired by most of the respondents (92.2%) (Q32).

The subjective degree of burden in attending hospitals to receive treatment (Q35) was neutral overall, and the acceptable upper limit for visiting hospitals was largely 1 or 3 h (92.9%) and was more than 5 h for only 2.0% of respondents in the case of visiting on a schedule of once every two weeks (Q36), while the upper limit slightly increased (e.g., from 2.0% to 5.95%) in the case of visiting once every 2–3 months (Q37), with a significant difference between answers to these questions ($p\text{-value} < 0.001$ in McNemar test).

Most of the respondents had concerns about ARIA (Likert scale 1 or 2 in 70.1%) (Q38), but had slightly less concern when it came to the observable symptoms of ARIA (Likert scale 1 or 2 in 54.8%) (Q39): there was a

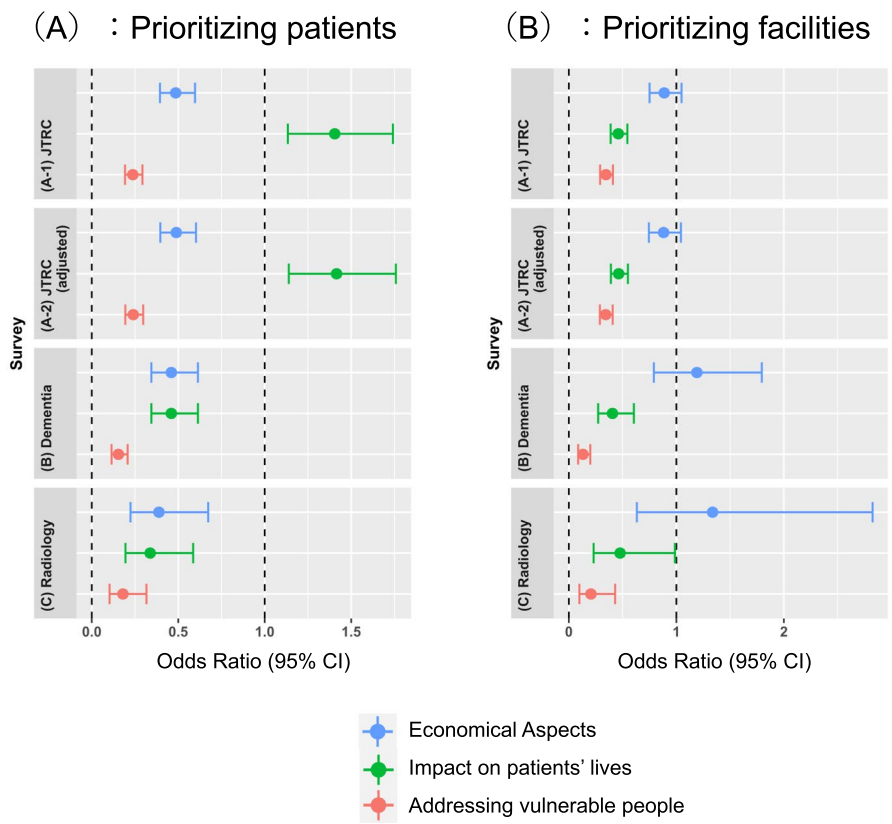

Fig. 3 Mixed logistic regression analysis for pros/cons about prioritizing patients or facilities in each dataset. Compared to the acceptance of prioritization in terms of medical rationale, economical aspects was consistently less likely to cause acceptance towards prioritizing patients (**A**, approximately 0.4–0.5 of OR) across the examined surveys, and addressing vulnerable individuals was the reason that consistently accompanied least likelihood to accept for prioritizing patients (**A**, approximately 0.2 of OR). Meanwhile, compared to the acceptance of prioritization in terms of medical rationale, addressing vulnerable people or the impact on patients' lives showed significantly lowered likelihood to accept for prioritizing facilities (**B**) across the examined surveys consistently, while the economical aspects did not show significant increase or decrease in OR as a focus to accept for facility prioritization (i.e., 95%CI overlapping with the OR = 1). Abbreviations: J-TRC, Japanese trial-ready cohort; CI, confidence interval

significant difference between answers to these questions (p-value < 0.001 in McNemar test).

The subjective financial burden of DMT cost was too heavy for the majority of respondents (Likert scale 1 or 2 in 75.3%) (Q40), but this degree of burden was not associated with their own co-payment rate (Q9) (Chi-square test p-value = 0.734). Among the potential barriers (Q46), treatment cost was cited as the profound reason that may force respondents to give up treatment (75.4%).

The majority of respondents (59.9%) became more interested in DMT treatment after taking the current survey (Q47), and the respondents wanted to undergo treatment as early as the preclinical AD (58.2%) or MCI (23.7%) stage (Q48). Overall, efficacy (60.9%), cost (65.5%), and adverse effects (71.9%) were the top three most concerning characteristics of DMT (Q49), even after information provision through the survey questionnaire. In contrast, the burden of attending hospital was a concern for only 25.1% of respondents.

Discussion

This study conducted an anonymous online survey using Google Forms among participants of the J-TRC webstudy [18, 19], a web-based registry designed to recruit individuals with preclinical AD [20]. We received responses from 2,050 individuals, primarily aged in their 50 s-70 s with unimpaired cognition. The perceptions of J-TRC respondents regarding the eligibility and efficacy of DMT differed slightly from those of specialists in dementia treatment or radiology. A majority of both J-TRC respondents and specialists expressed some degree of acceptance towards patient prioritization for DMT in the context of hypothetical resource constraints or other limitations. The study's strength lies in the execution of an integrative survey along with a large-scale clinical research (i.e., J-TRC webstudy), coupled with a comparative analysis of the findings against those from other surveys targeting medical specialists. The results could aid in identifying knowledge and perception disparities

between potential patients and healthcare providers, enhancing the delivery of patient information in clinical settings, and facilitating discussions on patient prioritization for DMT.

One of the most distinctive aspects of this study is the investigation into the acceptance of prioritization. The rationale for investigating this issue here is the potential constraints in the preparedness for actual DMT treatment provision, where substantial wait time have been a concern [9]. It will not be easily overcome due to the significant expenses involved. In the United States, the acquisition cost of lecanemab is $26,500 [27], and a similarly steep price had been anticipated in Japan. This was confirmed when the annual cost of lecanemab was set in December 2023 at approximately $20,000, based on an exchange rate of $1 to ¥150, for patients weighing 50 kg [7]. The financial burden of such costly treatments for the large number of potential patients has prompted concerns regarding its impact on the national budget [28]. It also appears impractical to expect that substantial national investment could be made sufficiently to establish a DMT treatment infrastructure capable of meeting the full spectrum of needs for AD therapy.

This study undertook a robust and diverse examination by comparing acceptance of patient prioritization between medical specialists and J-TRC online users. A high level of acceptance for prioritizing facilities was noted among dementia treatment specialists (85.7%), which is consistent with the OUG for lecanemab [13] that was issued by the Japanese authority in December 2023 subsequent to our survey. The OUG recommends prioritization of facilities and doctors for administering treatment. However, the acceptance of prioritization of patients was not unanimously high; it reached only approximately two-thirds at best in surveys directed at J-TRC participants, dementia treatment specialists, and radiology specialists. Shifting focus to addressing vulnerable people as a basis of prioritization most significantly decreased the likelihood of accepting patient treatment prioritization consistently in all surveys, whereas considering economic aspects resulted in a more moderate decrease in the likelihood of acceptance.

It is important to highlight that the specific content or direction of "prioritization" was not explicitly defined in the surveys; the questionnaire simply inquired about the respondents' impressions about the pros and cons of prioritization itself without specifying its particulars. Therefore, we need to interpret the results carefully. In terms of focusing on medical rationale, the likelihood of misinterpretation of "prioritizing patients based on medical rationale" would be low: "prioritizing patients based on medical rationale" would *not* generally be understood as administering treatment primarily to those expected to have *minimal* efficacy or *significant* adverse effects. This understanding is expected to hold true even among J-TRC webstudy participants, who are not medical professionals. Hence, we can infer that there is a relatively robust consensus on the acceptability of prioritizing patients who are more likely to experience *significant* efficacy or *fewer* adverse effects from treatment. This is compatible with previous studies investigating prioritization of patients with other non-urgent diseases, reporting that patient stratification based on disease severity is a frequently used method for prioritization [29].

Meanwhile, regarding economic aspects, impact on patients' lives, or addressing vulnerable populations, interpretations of "prioritization" may differ among individual respondents. Some may understand prioritization to mean giving precedence to those who meet certain conditions, while others may believe it should favor those who do not fulfill these conditions. For instance, although many respondents might conceive that prioritizing patients in terms of addressing vulnerability implies that those who are vulnerable should be given precedence, others may possibly interpret it in the opposite way, believing that such individuals should not be a priority. This potential variance in interpretation due to the lack of definitions necessitates a cautious approach to the analysis of the results. Consequently, discussions about patient prioritization, particularly with respect to vulnerable groups, must be approached with sensitivity, regardless of the presumed intent of the prioritization.

Beyond inferences made directly from the Odds Ratio (OR) value, it is also possible to deduce a hierarchy in the consensus regarding patient prioritization criteria: medical rationale is deemed most acceptable among the four examined aspects, followed by economic considerations and the focus on vulnerable populations. Moreover, the impact on patients' quality of life is considered more acceptable than addressing the needs of vulnerable groups. This hierarchy of acceptance is consistently reflected across different surveys (Fig. 3A), indicating that the detailed discussions on patient prioritization might be more fruitful if approached in this sequence.

The demographic profile of J-TRC respondents is an important basis for considering the generalizability of the current results. J-TRC respondents predominantly span individuals in their 50 s to 70 s, most of whom hold a bachelor's degree. They are largely cognitively unimpaired and about half are employed full-time or part-time. Additionally, a significant portion of respondents reported a parental history of dementia or AD. Approximately two-thirds of the participants reported experiencing a subjective decline in memory compared to the previous year. Considering the J-TRC study's focus and these characteristics, it can be inferred that many

respondents are likely to be well-educated individuals with a heightened interest in dementia treatment, possibly stemming from concerns about their own risk of developing AD. Consequently, the current survey may not completely capture the perceptions of the broader Japanese population. Nevertheless, the results of J-TRC online users were compared with those of other subpopulations in Japan, i.e., medical specialists in the fields of dementia treatment and radiology, which served to complement the external validity of the results obtained. The study provides valuable insights as the J-TRC participants are potentially more likely to become eligible patients or their family members than the general Japanese populace, given their generally higher level of interest in and commitment to DMT compared to the average.

Discrepancies were observed between J-TRC respondents and specialists regarding perceptions of DMT: J-TRC participants demonstrated less subjective knowledge about DMT (Q17) (coefficient -1.014), greater disappointment regarding DMT drug eligibility (Q19, Q20) (coefficients -0.660 and -0.657, respectively), and a slightly more positive impression of DMT drug efficacy (Q21) (coefficient + 0.1). Physicians should consider these differences when communicating with patients, as some individuals seeking DMT drugs in outpatient clinics may have overly optimistic expectations regarding the treatment's efficacy.

The package insert for lecanemab, published in the United States, mandates *APOE* testing for all patients prior to administering lecanemab. This is to assess the risk of developing ARIA [14]. In line with this, the latest clinical guideline issued in Japan in September 2023 regarding the testing of AD biomarkers [30] also supports conducting *APOE* testing given it is for the purpose of risk assessment prior to DMT administration. Despite initial uncertainties about the willingness of individuals in Japan to undergo *APOE* testing—considering it is a form of genetic testing—our study found a high acceptance rate for the testing. Specifically, 90.4% of respondents were willing to undergo the *APOE* test, especially if it were a precondition for treatment (44.6%) or if covered by health insurance (45.9%).

What is challenging in the implementation of *APOE* testing in the Japanese clinical setting is that it is currently not covered by health insurance, and there is no prospect of prompt coverage for it. While some out-of-insurance *APOE* testing services do exist, the provision of "mixed medical service"—a practice where insured and uninsured medical services are combined for the treatment of the same condition within a single facility—is strictly prohibited in Japan [31]. This restriction further complicates access to *APOE* testing, despite its recognized importance in the clinical management of DMTs. The inclusion of *APOE* testing under health insurance is keenly anticipated, as it would greatly facilitate the broader adoption of testing [32], which is a critical precursor to DMT treatment.

Furthermore, despite the lack of support from the guidelines [30], a significant proportion of respondents (45.7%) expressed a desire to undergo *APOE* testing even if it is not part of risk assessment for the administration of DMTs. This indicates that there is a notable demand for *APOE* testing, whether through out-of-insurance or direct-to-consumer services. Our prior research has shown that the level of patient information may be compromised in out-of-insurance services [32], which raises additional concerns regarding the practical implementation of *APOE* testing.

The OUG for lecanemab [13] recommends a certain degree of prioritization of facilities and doctors for administering treatment. In order to commence the administration of lecanemab for eligible patients, the OUG requires medical institutions to employ a minimum of two designated specialists, possess the capability to conduct cognitive assessments (MMSE and CDR), perform brain MRI scans at any given moment, and be prepared to provide necessary treatments in the event of adverse reactions, including ARIA. There is a concern that there may be a shortage of medical facilities that meet these requirements, especially in rural areas where a shortage of physicians has traditionally been noted. The variability in accessibility to medical facilities by geographic location within the country should also be examined in the future.

Our study has several limitations. Firstly, the respondents from the J-TRC are not representative of the entire Japanese population, nor do the specialist respondents represent all specialists within Japan. Moreover, they may not be representative of all J-TRC webstudy participants, as indicated in our previous report, which showed that those more engaged in online study activities (namely, those with higher motivation) are more likely to respond to this kind of survey [23]. Additionally, although we have compared three sets of survey data (i.e., J-TRC and two specialist groups) using questionnaire item texts that were only marginally different from each other, the interpretation of and response to the concept of 'prioritization' might vary slightly depending on the population examined, so that the answers regarding the advantages and disadvantages of prioritization may be based on qualitatively different foundations. Thirdly, since this anonymous study did not require respondents to log in with their Google accounts or enter their J-TRC credentials, we could not eliminate the possibility of duplicate responses from the same individuals. Lastly, at the time

of the survey, respondents had little knowledge of the requirements regarding eligible patients and treatment facilities as outlined in the OUG that was published subsequent to this survey. Consequently, it can be posited that the survey may have inquired about levels of preferences for conceptualized "prioritization" that did not take into account specific requirements. It might be necessary to conduct another survey based on specific OUGs.

In conclusion, this study employed an anonymous online survey distributed via Google Forms to participants of the J-TRC webstudy. The aim was to investigate the Japanese public's perception of DMT and related issues. Our findings offer insights into the discrepancies in knowledge and perception between potential patients and healthcare providers. This could enhance the delivery of patient information in clinical environments and inform the dialogue surrounding patient prioritization strategies.

Abbreviations

AD	Alzheimer's disease
J-TRC	Japanese trial-ready cohort
MCI	Mild cognitive impairment
CSF	Cerebrospinal fluid
PET	Positron emission tomography
CI	Confidence interval; IQR, interquartile range

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13195-024-01568-8.

Additional file 1. Questionnaire contents. The English-translated version of questionnaire explanations, questions, and answer choices.

Additional file 2. Respondent characteristics of surveys for specialists. These questions about specialist attributions have not been defined in coorperation with the survey to J-TRC web users. Majority of specialists in radiology belong to so-called "large hospital" (i.e., special functioning hospital, regional medical care support hospital, and clinical research core hospital) (51.8%), while approximately one-fourth of specialists in dementia treatment belong to the "large hospital" (27.5%). Region of respondent specialists reside are not confined to Kanto region (25.5–31.3%) unlike the J-TRC webstudy respondents.

Additional file 3. Summary of shared question results from the surveys. A summary of commonly designed questions (Q17-Q21, Q28, Q41-Q45). Compared to specialists in dementia treatment, J-TRC webstudy participants had less subjective knowledge about DMT (Q17). Meanwhile, J-TRC participants showed a more disappointing impression of the eligibility of DMT drugs than specialists in dementia treatment (Q19, Q20), while specialists in radiology had no difference in their impression of DMT eligibility compared to the specialists in dementia treatment. In terms of the degree of efficacy (Q21), J-TRC participants had a slightly positive impression than specialists in dementia treatment. Acceptance towards prioritization showed largely similar results both in J-TRC participants and specialists. For prioritization in a general term (Q41), allowing prioritizing both facilities and patients was the most prevalent choice selected either by J-TRC participants, specialists in dementia treatment, and specialists in radiology. Acceptance towards prioritization of facilities ([b] & [d]) was expressed by 52.4% of J-TRC respondents, 85.7% of dementia treatment specialists, and 76.2% of radiology specialists. Meanwhile, acceptance towards prioritization of patients ([c] & [d]) was expressed by 65.9% of J-TRC respondents, 67.6% of dementia treatment specialists, and 63.6% of radiology specialists.

Additional file 4. Summary of other question results from the survey to J-TRC users. The majority of respondents demonstrated a similar level of knowledge regarding both PET scans (Q22) and CSF analysis (Q24). However, half of the respondents (50.0%) expressed a preference for amyloid PET scans over CSF tests for determining eligibility for DMT drugs, while only a small percentage favored CSF tests over PET scans (2.3%). Additionally, a significant majority preferred that these tests be conducted at local facilities (68%). According to the survey to specialists in dementia treatment, which contributed to the results of this study, amyloid PET is available in approximately 46% of clinical settings where these specialists practice (question R16, data not shown). This indicates that nearly half of the potential Japanese patients for DMT may have no alternative but to utilize CSF testing, irrespective of their preference. The subjective perception of burdens associated with hospital visits for the treatment (Q35) was generally neutral. A significant majority of participants (92.9%) indicated that a 1 to 3-h visit every two weeks (Q36) was their maximum acceptable travel time. However, this upper limit marginally increased for visits scheduled once every 2 to 3 months (Q37), with a statistically significant difference observed between the responses to these two questions ($p < 0.001$, as determined by the McNemar test). These are specific figures of subjective upper limit in hospital visit based on Japanese traffic conditions. The development and approval of novel DMTs that require less frequent administration could expand the geographic reach of hospitals capable of providing care, thereby increasing the number of facilities where DMTs are available. The level of concern regarding ARIA among the majority of respondents diminished only slightly when they were presented with observable symptoms attributable to ARIA (i.e., the proportion of concerned individuals decreased from 70 to 55%). We suspect this attenuation in concern may be partly due to the patients' heightened anxiety, which could be provoked by undetailed explanations describing 'brain changes such as edema or hemorrhage' as side effects of medication. Using schematic illustrations that depict typical ARIA manifestations as the explanation of 'brain changes' may be beneficial.

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Authors' contributions
KS (first author): Conceptualization, Study Design, Data Acquisition, Data Curation, Analysis, Writing draft. YN: Conceptualization, Study Design, Data Acquisition, Review & Editing. RI, AI (fourth author), KS, KN, TA, SH, AI (9th author), KK, SA: Study Design, Data Acquisition, Review & Editing. T.I: Supervision. All authors read and approved the final manuscript.

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Availability of data and materials
Pseudonymized data will be considered for data sharing on reasonable request.

Declarations

Ethics approval and consent to participate
The J-TRC webstudy was approved by the University of Tokyo Graduate School of Medicine Institutional Ethics Committee (ID:2019132NI-(3)), and online informed consent was obtained from individual participants upon registration. The online survey was also approved by the local ethics committee.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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