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Views of stakeholders at risk for dementia about deep brain stimulation for cognition

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1. Introduction

Deep brain stimulation (DBS) has proven effective in treating epilepsy, movement disorders, like Parkinson disease (PD), dystonia, essential tremor, and has been investigated for treatment of other conditions, including depression, obsessive compulsive disorder, anorexia nervosa, post-traumatic stress disorder, and addiction [1]. The prospect of DBS as a treatment for Alzheimer's disease (AD) has also been explored. A systematic review in 2021 identified 16 human clinical studies of DBS in AD [2]. DBS at different brain targets (e.g., fornix, nucleus basalis of Meynert, ventral capsule/striatum) has shown mixed results [3–5]. While some in the field have expressed skepticism about the prospect of treating AD with neurostimulation [6], there is optimism that new stimulation paradigms (e.g., frequency, target, duration, laterality, current intensity, computation model-based stimulation pattern) may improve outcomes [7,8]. A search of clinicaltrials.gov in November 2022 found 11 planned or ongoing DBS trials for mild cognitive impairment (MCI), AD, or Parkinson disease dementia. DBS research for treatment of AD has been motivated in part by serendipitous discovery of cognitive benefits of DBS for other conditions [9] and the absence of highly effective pharmacotherapy [10].

The prospect of using DBS for treatment of AD or other dementias has raised ethical concerns [11–14]. One such concern has been whether "overstatements and speculative interpretations" from past studies promote unrealistic expectations in trial participants and whether risks of research participation are warranted [11]. Others have emphasized the challenge of achieving informed consent, issues of post-trial access to DBS, and whether research participants with dementia will expect clinical benefit (therapeutic misconception) [13] or the relative dearth of animal safety and efficacy data [15]. There are also questions surrounding the challenges of informed consent after initiation of a trial for DBS, both for new procedures and continued trial participation [14].

There is an increasing appreciation that ethical discourse around emerging neurotechnology should be informed by stakeholder input [16,17]. Engagement with stakeholders – prospective and current device users, family, clinicians, researchers, members of the general public – is important to understanding the benefits and risks of moving neurotechnologies, such as DBS, into new areas [18–22].

Stakeholder engagement about DBS for dementia has lagged behind other conditions. Most stakeholder research about neurostimulation for cognition has focused on enhancement of cognitively healthy groups [23,28] or does not include individuals most at risk of dementia [24]. Risk factors for future dementia include family history, biomarkers, and MCI [25,26]. Dunn et al. [27] conducted an online hypothetical vignette-based survey of 56 individuals at risk of dementia by family history, 60 caregivers of a person with dementia, and 124 controls about interest in participating in DBS and transcranial magnetic stimulation clinical trials for Alzheimer's disease and related dementias and found a trend toward higher willingness to participate among the dementia at-risk group. Online surveys have emerged as a common methodology for examining stakeholder perspectives on cognitive enhancement and treatment [23,24], whereas qualitative interviews, which allow for close study of complicated and undertheorized domains, like emerging neurotechnology [17] and research attitudes about experimental therapy in dementia [29], are underrepresented.

We conducted a qualitative interview study of individuals at risk of

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future dementia due to AD. We explored personal and familial experience with cognitive impairment as well as attitudes toward hypothetical future DBS devices affecting areas of cognition and behavior relevant to dementia – memory, language, executive function, visuospatial skills, and personality.

2. Methods and analysis

Participants at risk of future dementia due to family history, genetic testing, or MCI were recruited for this study using two rounds of Facebook advertisement. A dementia at-risk population is well-positioned to provide critical insight into potential opportunities and challenges related to the development of DBS for cognition and behavior. Online consent was obtained after participants passed an online cognitive screening test. This study was approved by the Oregon Health and Science University Institutional Review Board (IRB #22238).

Interviews were structured around five 2-min videos describing future DBS devices targeting areas of cognition and behavior relevant to dementia (short term memory, language, visuospatial function, executive function, and personality maintenance). A semi-structured interview guide, focused on participant impressions of each device was modeled on prior work exploring implantable neural device research [22,30] and iteratively refined over 2 months by all members of the research team. The interview guide was piloted with two individuals at risk of future dementia (Table 1 supplemental materials).

Between February 2021 and January 2022, 34 interviews, lasting 52–105 min (mean = 78 min), were conducted, for a total of 2645 min of recorded audio. Individuals who reported a diagnosis of MCI (n = 9, reported as M1-M9) were interviewed by a cognitive neurologist [EK]]; all others (n = 25, reported as N1–N25) were interviewed by [ID, AS or KM]. Weekly check-ins with the interviewers [EK, KM, AS, ID] refined question prompts and maintained consistency of interviews. Participants completed an online survey about participant demographics, subjective cognitive concerns [31], and personal concerns about developing AD [32].

Interviews were recorded via WebX and transcribed. Transcripts were reviewed for accuracy. A modified grounded theory approach to analysis was conducted by [EK and NM], using an iterative process of deductive application of interview guide categories and inductive identification of emerging themes from transcripts [33,34].

3. Results

The 34 participants represented a diverse range of ages, genders, races, and ethnicities, with groups endorsing categories of female (n = 24), Caucasian (n = 24), middle age (between 45 and 64 years; n = 17), and graduate level of education (n = 20) (Table 1). Five individuals endorsed knowing a family member or friend with a DBS.

Table 1
Demographics.

Age	n (%)
25–34	1 (2.9%)
35–44	3 (8.8%)
45–54	5 (14.7%)
55–64	12 (35.3%)
65–74	12 (35.3%)
75 <	1 (2.9%)
Gender	
Female	24 (70.6%)
Male	8 (23.5%)
Other	2 (5.9%)
Race/Ethnicity	
White/Caucasian	24 (70.6%)
Black or African American	2 (5.9%)
Asian or Pacific Islander	2 (5.9%)
Hispanic or Latino	2 (5.9%)
American Indian or Alaskan Native	1 (2.9%)
Two or More Races	2 (5.9%)
No Response	1 (2.9%)
Education	
Graduate-level degree	20 (58.8%)
Some college, but no degree	4 (11.8%)
4-year college degree	7 (20.6%)
High school diploma (or GED)	2 (5.9%)
2-year college degree	1 (2.9%)
Relationship	
Never married	3 (8.8%)
Married	24 (70.6%)
Widowed	2 (5.9%)
Divorced	5 (14.7%)

Table 2
Risk factors for future dementia.

Types of risks	n (%)
MCI (self-report)	
Yes	9 (26.5%)
No	22 (64.7%)
Don't know/unsure	3 (8.8%)
Cognitive challenges (self-report)	
Remembering recent events	13 (38.2%)
Planning and completing tasks	11 (32.4%)
Finding words	21 (61.8%)
Following maps or patterns	6 (17.6%)
Genetic test for dementia risk	
Yes	13 (38.2%)
Unsure	3 (8.8%)
No	18 (52.9%)
Cerebrospinal fluid dementia biomarkers	
Yes	3 (8.8%)
No	31 (91.2%)
Related to someone with dementia	
0 or unknown	9 (26.5%)
1	5 (14.7%)
2-3	15 (44.1%)
>4	5 (14.7%)
Positron emission tomography (amyloid) imaging	
Yes, positive results	1 (2.9%)
Yes, results unsure	1 (2.9%)
No	32 (94.1%)

4. Participant risk factors for future dementia

All participants had at least one known risk factor for development of future dementia (diagnosis of MCI, genetic or other diagnostic test, family history of dementia) (Table 2). Nine participants (27%) self-reported a previous MCI diagnosis and 61% endorsed subjective cognitive decline.

Participants described the impacts of cognitive impairments on their daily lives (Table 4 supplemental materials). Thirteen participants (32%) reported having a genetic test related to Alzheimer's disease risk (research study test (5), direct to consumer test (7), clinical test (1)). Twenty-five participants (73%) reported that a living or deceased first degree family member carried a diagnosis of dementia and over 50% of participants reported more than one family member with dementia. Six participants reported having two biological parents who carried a dementia diagnosis. The dementia of family members was characterized by impairment in different cognitive and behavioral domains (memory, language, executive function, visuospatial function, and personality) (Table 4 supplemental material).

5. Participant perception of at-risk status

Most participants in the study were concerned about developing AD (Table 3), with nearly half (n = 15, 44%) of participants being "very" concerned.

Given their at-risk status for dementia, some participants felt "resigned to it" (N22) or that decline was "sort of inevitable" (N7). One participant concluded:

Table 3
Participant concern about the future development of Alzheimer's Disease.

How concerned are you about personally developing Alzheimer's Disease?	n (%)
Very	15 (44.1%)
Somewhat	15 (44.1%)
Not very	3 (8.8%)
Not at all	1 (2.9%)

"Alzheimer's runs on both sides of my family. My dad died of it. My mom's in stage, um [does not specify]. Through 23andme, it showed I had two markers. So, I got one from each parent, one of my sisters has none, and the other one only has one. So, it means that I got [pause], I was the "lucky" one that got it. And I'm single, I'm single, never been married, have no kids. So, it's like, good [sigh], it's gonna be me against the world when it gets to that stage." (N16)

6. Attitudes toward DBS

After watching short video device descriptions, participants gave their first impressions of five different devices (Table 4). Some people were generally positive about devices or generally negative, but others were initially positive about some devices and negative or ambiguous about others (e.g., N6 was excited about a language device but skeptical about a memory device).

7. Hoped for benefits of a device: addressing the harms of dementia

Participants expressed hope that a neurostimulation device might mitigate dementia-related harms. As one participant noted: "I have seen the devastation it does to not just the person but the family as well … it has made me very open to … open minded to almost anything for the most part" (N9). Another noted:

"I'm terrified of losing my memory … I don't want to just forget everybody and just be … So, that scares the heck out of me. And I'm not one to sit back and see what happens." (N8)

Table 4
Select first impressions of cognitive/behavioral devices.

Device type	Positive	Negative	Ambiguous/ conflicted
Memory device	"very positive" (N5); "valuable" (N21); "good for anybody" (N22);	"an extreme measure" (M7); "a little creepy" (N3); "Are you even kidding me?" (N1).	"it sounds interesting" (N14); "generally positive … [but] gives me pause" (N21).
Language device	"I'm pretty excited about it. I think I need that right now" (N6); "Oh my gosh, that'd be fabulous […] Sign me up!" (N21).	"Really?" (M7); "I don't think that's of value" (N12); "No" (N24).	"It sounds interesting" (N14).
Visuospatial device	"it would really be good" (N16); "Generally positive" (N21).	"It's not one I would really be interested in." (N22) "It's invasive." (N24)	"I'm not as impressed." (N25)
Executive function device	"Thumbs up" (N1); "I like it" (N25).	"Suspicious" (N5); "Skepticism" (N7); "Strange" (N9).	"Intriguing" (N21).
Personality-maintaining device	"I'd absolutely be open to it" (N9); "I love it" (N21); "That would be huge" (N25).	"Wow. Oh, man" (N1) "unalterably opposed" (N7); "a little creepy" (N18).	"I think it's odd" (M6).

Participants described a range of harms associated with cognitive impairment, including harms related to independence, identity, relationships, stigma, family member quality of life, physical safety, and social isolation.

7.1. Improvement of daily functioning

Participants hoped that a device might restore, maintain, or enhance a person's daily functioning, such as "purchasing a car" (N5), "building things" (N5), take dog for a walk (N1), remembering to take pills (N15), remembering to be nice to grandchildren (N15), taking care of pets (N1, N16), and remembering to eat, shower, and launder clothes (N22). If it could "extend their ability to remain independent … it's a huge success" (N18). Others simply hoped that a device might reduce the kinds of unsafe behaviors they had witnessed in their family members, like leaving the stove on (N14) or driving unsafely (N21).

7.2. Maintain identity

Some expressed that the most significant benefit of a cognitive device would be allowing people to maintain their identity through the course of dementia. Participants often connected identity to memory. "Without our memories … you just lose who you are" (N14). Others framed memory-related identity concerns in terms of personality:

"[T]he worst part of losing your memory, is that you've lost you, who you are. This is the last part of losing your memory. It's the last part of you that goes. It's the personality, the zeal, the person that you used to be, dancing and playing the piano and singing or whatever it is that you do that is you." (N24)

Others focused on the significance of narrative for identity:

"[W]e have a narrative about ourselves in our own lives. That helps us … that helps direct our lives. And kind of helps us put our lives in context. And when you lose pieces of that, you lose part of, you know, you lose part of your story. It's like losing part of yourself." (N5)

7.3. Preservation of relationships

Participants hoped that an effective device might reduce damage to relationships between people with dementia and their family and caregivers. Some referenced the harm to relationships when a person with dementia lashes out, physically or verbally. One participant recounted her family's experience with dementia and then contemplated how she might one day mistreat her family. "[I]nstead of treating them with the love that I want to treat them with, that I, you know, might treat them badly" (N5). Others spoke poignantly of the pain of no longer being recognized by a family member with dementia and expressed that a device capable of preventing this would be "a blessing" (N25). One participant speculated that her mother would have pursued a device if she could have avoided this loss:

"I think if somebody would have told [my mom] that we can give you a device … and it would help … you know who you're around ….I think she would have jumped on that in a heartbeat. Because, I think for her, as such a social person and such a matriarch in our family, that was one of the hardest things for her was … not knowing people … not know her family, not know her grandkids … She would just cry and be like, "How come I don't know? There's something wrong with me." (M3)

The hopes expressed by interviewees were sometimes directed explicitly at the prospect of a future DBS device and at other times at DBS as representative of any potentially effective future intervention in dementia treatment.

8. Concerns about using neurostimulation for treatment of cognitive impairment

Participants' hopes were tempered by concerns, specifically concerns related to (1) physical invasiveness of devices, (2) cognition being too complex to treat with a device, and (3) the fraught ethical context of decision-making in dementia.

8.1. Physical invasiveness of devices is worrisome

Many expressed concerns about the physical invasiveness of devices, in terms of "health risks" (N22), "drilling a hole in my skull" (N12), or a device being "deep in the brain" (N5). For some, the risk of something going wrong was simply too great. "[O]ne tiny, one little misstep [in surgery] can mess things up pretty, pretty significantly" (N11). For a minority of participants, physical invasiveness made a neurostimulation device a non-starter, "just totally not worth it" (N24). For most others, the promised benefits would have to be likely and substantial to outweigh invasiveness concerns. "I would have to have a very high payoff to have my skull opened and an electrode put in my brain" (N10). Another comically remarked, "I have a decision-assisting device now [pointing to his wife] - and it's not invasive" (N10).

8.2. Cognition is too complicated to treat with a device

Participants were skeptical that a device could effectively treat cognitive impairment. Some thought that memory was too complex. "[T]here's, like, so many kinds of memory." Others expressed the view that memory is "not a video-tape" (N5); rather, it's a dynamic process. "[E]very time you remember something, you change it" (N15). Participants raised doubts that a device could treat such a moving target. Others pushed back against the conceit that a device could target impairment in just one cognitive domain (e.g., memory), given that there is so much "overlap" (N4) among cognitive areas (e.g., memory, personality, executive function). Participants worried about unintended consequences of stimulation, including the possibility that a device might "affect your ability to forget things you want to forget" (N12) or interfere with healthy processing of difficult memories. Participants offered examples of memories of traumatic experiences – the Holocaust (M8), sexual abuse (M3), and military deployment of family members (M4) – that might be made worse in some way by use of a cognitive device.

8.3. Decision to get a device is fraught in the setting of dementia

Participants worried that it might be difficult to find the appropriate "therapeutic window" (N12) for treating dementia with a device and that the optimum time to implant a device might vary from individual to individual. Many expressed concern about the decision-making capacity of people with dementia. Some referenced poor insight into the severity of illness (anosognosia) that makes decision-making difficult for people with dementia. "I don't know how good the patient is at being a judge of their own abilities, to know when is the appropriate time to try something like [a device]?" (N21) Another noted a kind of "irony" that "by the time you'd really need it … you might have difficulty making those kinds of decisions, right?" (N7) Some worried that a decision to get a device might be unduly influenced by others due to economic or caregiving demands, such as "making [it] easier to maintain, you know, to take care of them in a facility" (M3).

In sum, while some participants were more positively inclined to cognitive devices and others less so, the most common attitude was general support with reservations. This balance was well summarized by one participant: "[I]t's scary to think of something on your brain … but not scary enough to stop me from doing it" (N9).

9. Personal threshold for getting a cognitive stimulation device

Very few participants ruled out altogether the possibility of getting a device at some time in the future. Most were at least open to this possibility. Participants considered pros and cons, costs and benefits, both to them as future individuals with cognitive impairment and to family members or others who might be affected by their disease and need for care. Participants shared how they viewed their threshold for pursuing implantable devices for treating cognitive and behavioral symptoms in the future.

9.1. Proven safe and effective

Most participants offered qualified openness to getting a future device if devices showed evidence of effectiveness. One participant noted interest "if they were well tested, and they seem to be effective in the risk-benefit analysis" (N7). Another expressed that "I would need to see data about the success of an implant" (N11). In large part, the desire for evidence was related to concerns about risk: "What is the failure rate? What is the success rate? What if you get it, and then later it fails, or just doesn't work very well?" (N20). One participant summarized the concern about risk: "What kinds of risks are you taking … could this be fatal? Could this be … could this turn you into a vegetable?" (N3). In addition, participants were curious about how long a positive effect of DBS would last and whether future surgeries would be needed.

9.2. No viable work-arounds for cognitive impairments

The threshold for considering a device was related to whether there were ways to cope with or accommodate impairments in cognition. Participants noted ways that people do or could compensate for cognitive challenges, including internet-connected cell phones to search for people's names (M2), digital calendars (N7) or alarms (M7) to aid remembering tasks or appointments, ridesharing services ("Ubers" (N19, N24)) or "cars that drive themselves" (N7)) to provide transportation, and automated door locks (N7) for physical safety. Participants offered that relying on family and friends was a common (and preferred (N7, N22) way to compensate for cognitive challenges, for example, to help drive, cook, clean, or order at a restaurant (N22) or to be a "wingman … for coming up with names of people that you know" (N15). Participants recognized limits to relying on assistive tools or caregivers to compensate for cognitive decline, especially in the circumstance of geographic (N2) or social isolation (N16), and offered that there might come a point at which an implanted device was a preferred option.

9.3. Device specifically targets a cognitive or behavioral area of personal concern

For many participants, the threshold for considering a device depended on which cognitive or behavioral domain a device would target. Participants had a lower threshold for considering a device targeting memory changes, and a comparatively high threshold for considering a device that treated visuospatial, language or executive dysfunction. The lower threshold for a memory device was related to the connections between memory and the ability to "live independently" (N3), to maintain relationships (e.g., remember "names and faces" (N2)), and to preserve personhood (N6). One participant put this bluntly:

> "[I]f it was my husband and my daughter, if I had that incident like, "Who are you?" Yeah. If it wasn't too late, then I'd get [a device implanted] instantly, right?" (N12)

The threshold for getting a device to treat language, executive, or visuospatial impairments was generally higher. Participants stressed that mild word-finding or occasional slips in conversation would not be

enough to meet their threshold, nor would problems with everyday decision-making (e.g., following a recipe) or performing routine tasks (e.g., driving).

Some participants had a low threshold for the personality-maintaining device, particularly if family members had experienced personality changes associated with physically or verbally aggressive behavior:

> "[I]f I was starting to [be] … abusive to family members, if I was starting to alienate family members with paranoia or verbal abuse or anger or if I was, you know, acting physically aggressive towards them […] I would probably be willing to take on some considerable risks to have a device [to treat] that" (N5).

Other participants found the prospect of a personality maintaining device confusing or disconcerting and expressed a high threshold for getting such a device.

10. Discussion

Although DBS is being investigated for the treatment of dementia [2], stakeholder views have been underexplored [27]. The current study examines how individuals at risk of dementia understand and view DBS as a potential treatment. The key findings of this study are that: (1) the harmful effects of dementia, whether witnessed as family members or anticipated by at-risk individuals, inform understanding of how DBS might work and its potential benefits; (2) at-risk individuals weigh potential benefits of DBS against concerns about "physical invasiveness", the complexity of treating cognition with a device, and the fraught ethical context of medical decision-making about high risk/high reward interventions in a progressive disease affecting decisional capacity; and (3) at-risk individuals support research to develop neurostimulation therapies for dementia, but their threshold for personally considering a future device is moderated by a desire for established safety and efficacy, a preference for targeting some domains of cognition or behavior (memory) over others (language, visuospatial, executive), and a reluctance to undergo a surgical option if other forms of assistance are available.

There is increasing interest in understanding attitudes toward research in populations at risk of dementia. Attitudes toward pharmacologic or other interventions (e.g., stem cell transplant [29]) have been studied in at-risk populations, including those who have participated in multiple Alzheimer's disease clinical trials [35]. The current study found that at-risk individuals used their first-hand knowledge of the harms of dementia – undermined independence, relationships, and sense of self, among others – to inform their views. Participants recounted detailed, and often heartbreaking, stories of the effects that dementia had on their loved ones. Even though participants were skeptical that devices would be as safe or effective as hoped, the self-perceived threat of developing dementia led participants to be open to the possibility of personally using a future DBS device.

Implanted neural devices are often viewed by patients and clinicians as higher risk interventions than pharmacotherapy, but worth the risk in certain situations, such as treatment resistance in epilepsy [36] or depression [37]. In the context of developing DBS for novel indications, like AD, understanding the thresholds at which potential end users of devices would consider DBS, if they would consider it at all, is important. Such thresholds inform whether DBS for AD (or other dementias) should be investigated at all, and if so, who would be potential beneficiaries and what benefits would be needed for DBS to be considered worth the surgical and other risks. This highlights the importance of attending to robust and dementia-specific informed consent practices, including the incorporation of family members.

A key threshold identified in the current study is the absence of alternative therapies in AD. Development of pharmacologic and behavioral interventions for AD has a disappointing history [10], though new pharmacologic approaches, such as immunotherapy, offer promise [38]. In light of this history – and personal experience with the physical and emotional challenges of caring for family members with dementia – it is perhaps unsurprising that participants were at least "open" to the possibility of a future DBS device for themselves. Still, we found evidence that there were limits to this openness. If work-arounds for cognitive impairment, such as assistive technologies or reliable loved ones who can step in and help, are not available, the openness to considering DBS increases. An important take-away, then, is that a technological solution may not be always preferred. At minimum, research on cognitive and behavioral devices should go hand in hand with research on ways to assist people with dementia and their loved ones as they navigate progressive cognitive decline and not come at the expense of developing dementia-friendly environments [39] or providing better economic and social support for caregivers of people with dementia [40].

11. Limitations

While qualitative research does not aim to be representative but to explore an undertheorized space, it is possible that relevant experiences were missed or unappreciated due to an unintentionally disproportionate representation of female gender, White race, and high education level. The study relied on participant self-report of an MCI diagnosis, genetic and biomarker testing results, and family history of dementia. The significance of possible inaccurate reporting of actual dementia risk is mitigated by findings of high perception of risk. Researchers were careful to distinguish Alzheimer's disease as a cause of dementia from dementia as a clinical syndrome, but did not correct any participant misunderstandings, and as such results of the study must be interpreted in light of a lay understanding. Although the study created educational videos about DBS for cognition and behavior, including descriptions of neurosurgery, it is possible that interviewees did not understand DBS devices sufficiently for them to distinguish between possible and unrealistic effectiveness of near-term devices.

12. Conclusion

Much work still needs to be done to understand the perspectives of stakeholder groups in relation to DBS and dementia. The current study demonstrates that qualitative research with stakeholders at risk of dementia is valuable for understanding future benefits and risks of DBS as a cognitive therapy. Groups at risk of dementia may be open to considering DBS therapy, but their concerns will need to be addressed. Understanding these concerns will require centering stakeholder engagement around clinically relevant cognitive and neurobehavioral abilities and disabilities (e.g., memory, language, executive function, visuospatial, and personality). Since study outcomes in future clinical trials in DBS are likely to measure along existing clinical categories and schemas, developing end user engagement methods that can track these categories and connect these to the lived experience of people with dementia or people caring for those with dementia has value.

CRediT authorship contribution statement

Eran Klein: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Writing - original draft, Supervision, Writing - review & editing, Project administration, Funding acquisition. **Natalia Montes**: Data curation, Validation, Formal analysis, Writing - original draft, Writing - review & editing. **Ishan Dasgupta**: Conceptualization, Investigation, Methodology, Resources, Writing - review & editing. **Kate MacDuffie**: Investigation, Methodology, Writing – Review & Editing. **Andreas Schönau**: Validation, Formal analysis, Investigation. Garrett Flynn: Methodology, Resources, Writing - review & editing. **Dong Song**: Conceptualization, Funding acquisition, Writing - review & editing. **Sara Goering**: Conceptualization, Supervision, Writing - review & editing, Project administration, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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