Articles

Patient Requests for Off-Label Bioprediction of Dementia

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Abstract: In 2012, the FDA approved for the differential diagnosis of Alzheimer's disease a brain-imaging technology, Amyvid-PET (aka florbetapir-PET), capable of non-invasively estimating the burden of amyloid plaques; this approval for one indication renders the technology a candidate for off-label use for another indication according to a physician's judgment. What should a physician do if an educated, pro-active, and concerned patient requests off-label use of Amyvid-PET to help her estimate the likelihood that her mild memory complaints are "just normal aging" or are likely to profoundly worsen? I consider reasons that a physician might justify denial of such a request, including concerns of safety, uncertain benefit, and fair resource allocation, but cautiously conclude that there may be certain cases where off-label bioprediction would be permissible.

Keywords: neuroethics; biomarkers; Alzheimers disease; florbetapir-PET; off-label use

If a person seeks a clinician's help to predict the likelihood of developing dementia, is there a scenario in which it would be acceptable for the clinician to use technologies "off label" in order to do so? Some clinicians may have already encountered such a request; others may have imagined the possibility. Here, we consider the following hypothetical request for bioprediction:

> JD, a 65-year-old primary care physician, presents with a chief concern of memory loss, seeking a referral to neurology. She acknowledges that her current symptoms are mild but voices her desire to become more informed about the likelihood that her symptoms are "just normal aging" or evidence of an early stage of Alzheimer's disease. She would like to discuss the possibility of using a brain-imaging technique off label to better estimate her risk of Alzheimer's disease. She explains that she has been following the amassing evidence that amyloid imaging can enable a rough estimation of the risk of developing Alzheimer's disease; she notes that one of these techniques to image amyloid beta plaques in the brain was approved by the FDA in 2012 for another indication, and thus it would be clinically permitted to use it off label for the purpose of risk estimation. Becoming better informed of her risk of dementia, she continues, would enable her better to plan for the future while she still has the time and cognitive capacity to plan effectively.

Though JD's case is hypothetical, the technological and regulatory elements that would enable the possibility of off-label bioprediction of dementia are real. In 2012, noninvasive amyloid imaging ceased to be relegated to research protocols when regulatory bodies in the United States and EU granted the first approval of a technology, Amyvid PET (aka florbetapir PET), for use in the differential diagnosis of Alzheimer's disease (AD).[1] There is also an accumulating body of work

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investigating the usefulness of Amyvid PET intensity as a biomarker to estimate the risk of future cognitive decline due to Alzheimer's pathology.[2]

Though this biopredictive science is still evolving, proactive and concerned patients (especially, perhaps, clinicians themselves) are likely to make the connection, as JD does, that FDA approval of florbetapir PET for one indication would render it legally permissible for a physician to choose to use it for another indication (e.g., as a probability estimator of cognitive decline)—that is, to choose to use it off label—according to clinical judgement. The plausibility of patients making this connection is supported by the observation that much of the research on the use of amyloid imaging for bioprediction is open access and is well covered by the media by virtue of the fact that it concerns a medical condition under an especially bright social spotlight—indeed, few medical conditions have the honor of being mentioned by name in a president's state of the union address, as AD was in 2013. Requests for off-label bioprediction of dementia, therefore, are likely to be increasingly encountered and consequently deserve systematic moral consideration by both generalists and neurologists.

I suspect that the initial stance of many clinicians is a cautionary one (as was my own): that such requests for off-label bioprediction should probably not be granted. I therefore consider justifications by which a clinician might deny a request. I frame these potential justifications loosely on a principle-based approach to ethics with which many clinicians are already familiar, and which is composed of autonomy, nonmaleficence, beneficence, and justice.[3] I show that some of the knockdown arguments against off-label bioprediction, such as the uncertainty inherent in the risk estimations, are not as knockdown as they appear and through this analysis raise the possibility that there might be a type of patient for whom off-label bioprediction might be permissible. Though this discussion is related to previous work on the ethics of returning imaging biomarker status in primary prevention trials of AD such as the A4 trial,[4] I hope to clear enough ground for clinicians to reach their own reflective equilibrium about bioprediction of AD in the murky gray of off-label use in the clinic.

Autonomy Justifications

A clinician might deny JD's request if she felt that JD was incompetent, uninformed, or coerced. Although competence is often a concern in dementia medicine, competence would normally be assumed in a person like JD who has not developed significant cognitive impairment and is not so (unreasonably) worried about the possibility of developing AD as to qualify for a mental disorder. A clinician might question whether it is possible for JD to be informed *enough* to make an informed decision to undergo florbetapir PET, because its reliability and predictive power has not been assessed in clinical trials. This sort of lack of direct clinical trial data, however, is the rule, not the exception, in decisionmaking about *off-label* treatments or tests, and thus if off-label use is *generally* permissible, lack of this information alone cannot render this *specific* instance of off-label medicine impermissible. Although care should be taken to guard against misunderstanding, a patient can be sufficiently informed about the extent and quality of the evidence supporting off-label use, and one would hope that JD, herself a physician, would be capable of this sort of understanding. Though AD is often framed in terms of burden on caregivers and consequently many patients who seek to ascertain their risk of the

disease may do so in hopes of minimizing the risk of burdening others, these external influences would rarely if ever be so overpowering as to qualify as coercive.

Although respect for autonomy supports a right to *refuse* a medical test (freedom from interference), however, it does not entail positive claims on others,[5] such as *demanding* to be given florbetapir PET; thus respect for autonomy does not require the clinician to provide access to bioprediction. An alternate reason to refuse giving florbetapir PET is if by performing the procedure the clinician would risk causing a categorically unacceptable harm—that is, violating a principle of nonmaleficence.

Nonmaleficence Justifications

One function of the principle of nonmaleficence is to identify categorically unacceptable harms—that is, harms that, if present, would trump any weighing of risks and benefits. Discussions of the potential harms of florbetapir PET have focused primarily on the psychological disvalue of learning that one is at increased risk, especially if one misinterprets the risk as deterministic rather than probabilistic. Other risks include the radiation exposure from the PET-CT (which varies by institution and technician) and risk of redness, itching, or pain from an allergic reaction at the radioligand injection site. None of these risks are of such large magnitude or quality, however, that florbetapir PET would be *categorically* excluded by a principle of nonmaleficence; rather, they should be weighed against the value to the individual patient of gaining the predictive information. In regards to the potential psychological harms of an unfavorable risk estimate, moreover, the REVEAL study showed that genetic risk status can be disclosed with proper counseling without increasing anxiety symptoms, and although some voice concern that the risk of psychological harm is greater with imaging as compared to genetic biomarkers,[6] this remains an untested empirical claim. Finally, if JD pointed out that healthy individuals are permitted to undergo PET-CT for research (*with no clinical benefit*), take jobs with occupational radiation exposures, or enroll in the A4 trial, in which they both undergo PET-CT and learn their dementia risk status, then it would be hard to claim that the potential harms of off-label florbetapir PET are categorically unacceptable.

Even in the absence of categorically unacceptable harm, however, clinicians might refuse off-label use of florbetapir PET if it is judged to not be in JD's best interests—that is, if it falls afoul with the principle of beneficence.

Beneficence Justifications

The principle of beneficence is often interpreted as a duty to act in a patient's best interests according to the sum of risks and benefits. In the absence of preventive treatments for AD, a clinician might question whether JD would benefit from florbetapir PET, as any resultant risk information would not change her medical management. It is especially important in considering JD's request, however, not to construe best interests in a narrow clinical sense. Information about risk of AD can, even in the absence of treatments, enhance autonomy and well-being. It can enable one to better act as an effective planning agent according to one's own concept of well-being. Financial planning and decisions about when and where to retire and about whether to spend time traveling, with family, or writing a lengthy

memoir all depend on implicit judgments about the probability that we will have a certain length of future mental competence.

A clinician might reasonably be concerned about the value of florbetapir PET to inform this sort of long-term life planning, however, because its reliability as a predictive tool is supported only by preliminary evidence. JD might acknowledge this limitation but point out that the popularity of the Weather Channel clearly indicates that predictive information can often be useful despite significant uncertainty. Moreover, the quality of the risk prediction from imaging may very likely be superior to the quality of that from the tools on which individuals like JD currently rely: *their own biases and gut instincts*. With the social spotlight on AD, it may even be the case that individuals are biased toward an *overestimation* of their risk of developing AD and thus would benefit from a negative PET scan, as it might help reduce such overestimation.

Many clinicians might have an intuition that off-label bioprediction would be more in JD's interests if she waits and her memory complaints worsen. But the realization of the benefits of bioprediction through the reorientation of life plans requires sufficient time, resources, and cognitive faculties. Though the current strength of the evidence of florbetapir PET's predictive value may increase in proportion to the pretest probability of AD,[7] the time and cognitive capacities left to an individual to effectively make life adjustments decrease; thus clinicians must balance uncertainty with personal utility.

Justice Justifications

Even if a clinician judged off-label use to be in JD's best interests, a clinician might deny the request if he thought it would lead to an injustice. Although concerns of distributive justice might arise in a public healthcare system if others could benefit more from the money that would be spent on florbetapir PET, this concern is weak if JD were willing to pay privately or purchased a private insurance plan that agreed to cover the cost; this could actually bring *more resources into hospitals* that could contribute to bettering the care of the worst off. Although a monetary barrier to accessing bioprediction of AD would put it beyond the reach of those not already well-off, one could argue that allowing access would benefit some while harming no one. Some might further argue that the risk/benefit calculus of biopredictive information may change depending on whether an individual has the financial resources to efficiently make life adjustments (some do not have the option of retiring early). In the future, the cost of bioprediction may rapidly decline. For example, in 2015, researchers at the Mayo Clinic developed an algorithm based on clinical, neuropsychological, and demographic parameters that could aid in the estimation of the risk that cognitively normal individuals would develop mild cognitive impairment.[8] The cost of such actuarial methods is determined only by the time needed to correctly input the relevant variables and to discuss with JD the meaning of the results.

Toward Responsible Off-Label Bioprediction

The future of our mental capacities is integral to planning our lives, but we currently have little on which to make predictions of that future. Because both the value and acceptable uncertainty of predictions increase the earlier they are made,

in some cases we might hit a sweet spot where bioprediction of AD is in a patient's best interests, a possibility that becomes increasingly likely as the evidence builds for the predictive validity of florbetapir PET and as predictive algorithms are refined. The possibility of a scenario in which off-label use of florbetapir PET or predictive algorithms should reasonably be permitted suggests that clinicians should consider such requests carefully on a case-by-case basis rather than instituting a blanket prohibition.

Notes

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