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Hypothesis

# Individual Patient Research (IPR) Outcomes with Alzheimer's Disease: The Psycho-neuro-immune Viewpoint

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**Abstract:**
Traditional research in the health sciences has involved control and experimental groups of patients, and descriptive and inferential statistical analyses performed on the measurements obtained from the samples in each group. As the novel model of translational healthcare, which integrates translational research and translational effectiveness, becomes increasingly established in modern contemporary medicine, healthcare continues to evolve into a model of care that is evidence-based, effectiveness-focused and patient-centered. Patient-centered care requires the timely and critical development and validation of a new research paradigm, which is referred to as "individual patient research (IPR)", as opposed as the customary group research approach. That is to say, research in geriatric disease conditions, such as Alzheimer's Disease (AD) must be performed from the viewpoint of individual patient research outcomes, and individual patient data analysis. Here, we discuss IPR in patients with AD in the context of the best available research evidence that indicates psychological symptoms, endocrine deregulation, and immune alterations in AD. We propose a clinical adaptive cluster randomized stepped wedge blinded controlled trial, with sequential with sequential roll-out of an evidence-based intervention in a crossover paradigm.

**Keywords:** Individual patient research (IPR), Alzheimer's disease (AD), hypothalamic pituitary adrenal axis (HPA), cell mediated immunity (CMI), psychoneuroimmunology, comparative effectiveness research (CER)

**Background:**
The Affordable Care Act, passed by Congress and signed into law by President Obama on March 23, 2010, and further upheld by the US Supreme Court on June 28, 2012 is the health care law of the land: It has, over the past 6 years, proffered many benefits to millions of Americans. But, it is by no means perfect, and in fact has carried forward hardship to another significant segment of the US population. Whereas, it demands additional concerted work toward its improvement, it, overall, has transformed the views of the scientific community about how healthcare research and delivery should be brought forth. The concerted forces that led to this legislation included a trend toward "translational research". Originally in the early 1990's, the term indicated work that spanned across (i.e., that "translated across") different types of medical fields, from immunology to neurosciences, such as for example, "psychoneuroimmunology" **[1]**, which defines and characterizes the intertwined cross-regulatory processes among the psychoneuroendocrine and the immune systems.

The term then evolved into a bidirectional continuum by which biopsies obtained from the patient are studied and characterized in the laboratory, and the elucidation of the fundamental biology and pathological mechanisms thus elucidated are communicated back to the clinical for prompt intervention directly on the patient who provided the biopsy. Thus, translational research by its very nature is patient-centered. Research in the health sciences has produced a plethora of new knowledge about disease processes and a vast armamentarium of possible interventions for any. It thus has become increasingly prohibitive for clinicians to determine which intervention might be best for a given patient. Thence **[2]** emerged evidence-based medicine, and the current conceptualization of translational effectiveness, as the product of research synthesis and

comparative effectiveness research for documenting, in the form of systematic reviews that report the consensus of best evidence base (BEB) for ensuring cost- and benefit effectiveness **[3,4]**.

Contemporary translational science for healthcare consists of a continuum from translational research (T1) – the transfer of knowledge from basic research to the clinical domain – to translational effectiveness (T2) – the identification and dissemination of BEB to practice settings and communities of stakeholders. Translational healthcare strengthens the array of knowledge available for academicians, the integration of multiple fields of biomedicine, and the drive toward bettering IPR, and simultaneously optimizes patient-clinician communication and patient-care delivery. T1 and T2 together optimize evidence-based, effectiveness-focused and patient-centered care, as articulated in the Affordable Care Act-2010.

Patient-centered care tailors healthcare in an articulated manner that requires patient-centered outcomes of research and evaluation. To encourage patient centered research in healthcare, and as a direct product of the Affordable Care Act-2010, the Patient-Centered Outcomes Research Institute (PCORI) was established. PCORI sets the methodological standards and guidelines in patient-centered outcomes research (i.e., individual patient research, IPR), prioritizes patient-centered outcomes research questions, obtains and disseminates BEB consensus, and responds to specific critiques, input and suggestions from the stakeholders. In the context of geriatric research, we propose here the hypothesis that timely and critical new information about the pathological spectrum that afflicts patients with AD systemically can be obtained using the IPR paradigm.

**Methodology**

*IPR Protocol:*

Psychological symptoms of agitation, aggression and anxiety, and endocrine deregulation, including the hypothalamus-pituitary-adrenal (HPA), characterize patients with AD, as well as alterations in cell-mediated immune (CMI) surveillance **[5-11].** The cross-regulation between the psychoneuroendocrine and the immune systems [**12-15**], and specifically HPA-CMI interactions, have not been investigated to date in patients with AD with clinically relevant psychological symptoms.

One possible avenue of psychoneuroimmune research in this subgroup of patients with AD involves dynamic and static challenges of the HPA axis, with IPR outcomes that include pituitary and adrenocortical hormones as well as certain CMI functional and phenotypic responses. For example in a repeated measures experimental design, subjects will act as their own controls. The dynamic challenge of the HPA axis will involve intravenous administration of ovine corticotropin releasing factor (1 ug/kg, i.v., 11:00 PM). The static challenge of the HPA axis will simply result from oral administration of the synthetic glucocorticoid dexamethasone (5 mg, PO, 11:00 PM).

*IPR Outcome Measures:*

IPR outcome measures can be salivary and plasma cortisol, plasma adrenocorticotropin hormone, and plasma and salivary cytokines levels (e.g., interleukin-6). Certain CMI functional responses can be tested *in vitro* with isolated peripheral blood mononuclear cells (e.g., stimulation with phytohemagglutinin - 5 ug/ml, 72h - for T cells, or with lipopysaccharide - 5 ug/ml, 72h - for myeloid cells), as well as the distribution of lymphocyte subpopulations by dual- or tri-color flow cytometry (e.g., naïve [CD45RA+CD4+] vs. memory T cells [CD45RO+CD4+]) **[14,15]**.

To ensure effectiveness, which includes lowering risk and prompt management of side-effects, the study must be performed in the context of a clinical research center Corticotropin releasing factor can lead to dizziness, fainting, nausea, vomiting, flushing, slight fever, or slight unease. No side effects result from dexamethasone, except some queasiness.

Expectations are that HPA-CMI alterations will be most evident in AD patients with psychological symptomatology. Therefore, stress and anxiety state of each patient should be monitored by the State-Trait Anxiety Inventory [**16]**. The Stroop [**17**] test for executive functions [**18**] is not *per se* a measure anxiety, but performance on the Stroop is impacted by anxiety. The Stroop quantifies the patients' difference in selective attention capacity and skills, and their processing speed ability. It provides a neuro-psychological glimpse on the patients' psycho-cognitive executive processing function, and is informative for patients with certain neurological abnormalities [**18**].

*IPR Data Analysis*

Three baseline samples of peripheral venous blood and whole saliva, obtained simply by presenting the subjects with a cut half lemon, which triggers salivation, must be obtained in EDTA- and protease inhibitors-coated tubes at the onset of the study (evening of day 1). Repeated measures samples should be collected in the same manner at 4:30 PM, 5:00 PM and 5:30 PM of day 2.

For each subjects, baseline measurements can be processed as means $\pm$ standard deviation. A difference, delta (D) is obtained at each repeated measures time point. For example: salivary interleukin-6 data would be rendered for each patient as D1, corresponding to its level at the 4:30 PM time point minus the mean level obtained at baseline, D2, corresponding to its level at the 5:00 PM time point minus the mean level obtained at baseline; and D3, corresponding to its level at the 5:30 PM time point minus the mean level obtained at baseline. The IPR data of the proposed study will be summarized for each individual patient as the set of D1, D2, and D3 for each HPA and each CMI repeated measures.

Analysis of these data will require repeated measure ANOVA, with Newman-Keuls post-hoc comparisons and Bonferroni corrections for comparative purposes. For predictive purposes integrating other

patient characteristics in the model, such as stage of AD, anxiety scores, Stroop scores, gender, age, etc., analysis will be performed by hierarchical multiple regression.

**Discussion**:
The purpose of this hypothetical study is two-fold: (1) Firstly, it serves as a model design, methodology and data analysis for individual patient research in general, and specifically in patients with AD; (2) Secondly, and perhaps more importantly, it can serve a Proof of Concept or Proof of Mechanism project to establish the psycho-neuro-endocrine-immuno-pathology of AD.

In that respect, the data produced by the hypothetical clinical research described here can lay the foundations for an adaptive cluster randomized stepped wedge blinded controlled trial [**20**], that will involve sequential roll-out of an evidence-based intervention in a crossover paradigm. The different clusters (i.e., ambulatory clinics of a practice-based research network) will cross over and switch treatments at different time points. The first time point must yield baseline measurements for each patient individually, as none of the clusters will be receiving the experimental intervention. At subsequent time points, clusters will switch over, following random ordering, and measurements would be obtained from each patient and analyzed as above as D's. Within each cluster, patients will be randomized, thus yielding a cluster randomized stepped wedge blinded controlled trial. In a design such as this, all patients eventually receive the intervention, ensuring adequate power, equipoise as well as benefit- and cost-effectiveness.

**Conclusion:**
In conclusion, similar to the adaptation and survival mechanism nature has intended for the success of species, we must adapt and evolve our clinical research tools from group statistics to individual patient data analysis, as dictated by modern translational science - the two pillars of which, translational research (T1) and translational effectiveness (T2), and supported and dependents upon dissemination of BEB and increased health literacy of patients, clinicians, and stakeholders –, and legislated the Affordable Care Act-2010. In that vein, we provided here a hypothetical study that exemplifies the culmination of translational science and IPR in the context of pragmatic translational science in gerontology in general and geriatric patients with AD in particular.

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