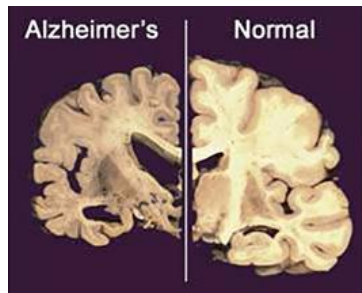


LymPro Test™: The Immune-based Blood Test for Alzheimer's Disease (AD) Diagnosis



Brain atrophy in AD due to neuron loss

What is the Value of Knowing?

...because patients and their families deserve to know an accurate diagnosis with more certainty so they can plan their futures and select targeted treatments.

What is the LymPro Test?

LymPro is a blood test that reflects a key neuropathology found in the brains of patients with AD. Unlike other biomarker tests, LymPro measures alterations in immune cell cycle control in peripheral white blood cells rather than the presence of abnormal versions of β -amyloid and/or tau protein in the brain, CSF or blood.

LymPro takes advantage of the discovery that control of the neuronal cell cycle in AD patients is deranged, and that this Cell Cycle Dysfunction (CCD) is mirrored in circulating lymphocytes, suggesting that blood-based assessment of CCD may be a useful proxy for autopsy-based diagnoses.

LymPro: Value Proposition in AD

- To serve as a valid surrogate for AD brain pathology before autopsy
- To increase accuracy of clinical diagnosis of AD by physician experts (currently ~70% in dementia, ~50% in MCI)
- To make testing cost-effective, convenient, easily tolerated, and widely available
- To identify AD patients for research

The Biological Concept Behind CCD

Unlike most cell types in the adult human body (including lymphocytes) that continue to divide to make new cells during the cell cycle, the brain's mature neurons have control mechanisms that prevent cell division and proliferation. However, in AD there is evidence of CCD: many neurons with extra chromosome segments ([hyperploidy](#)) ([Figure 1](#)) and [inappropriate expression](#) of cell cycle-associated proteins (CDK, Cyclin) ([Figure 2](#)) are found in brains of patients with AD relative to healthy controls. These changes ultimately lead to [neuronal death and brain shrinkage](#).

What Does the LymPro Test Measure?

The LymPro assay measures the expression of CD69, a cell surface protein present on lymphocyte populations that have been triggered to enter the cell cycle by [mitogenic stimulation](#). Analysis via a proprietary algorithm is used to determine whether there is evidence of [altered CD69 expression](#) that reflects either normal cell cycle or CCD in lymphocytes.

How Is the LymPro Test Performed?

A routine venous blood sample is collected and sent to a central laboratory for analysis of cell types and CD69 levels using flow cytometry ([see Figures 3 and 4](#)). A proprietary algorithm is applied to derive a LymPro score ("Stimulation Index").

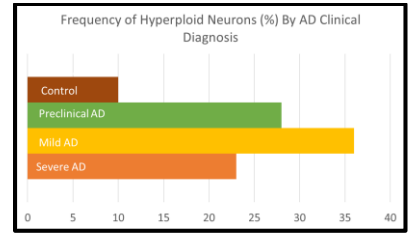


Figure 1: Hyperploidy in AD brain (redrawn from Arendt et al, 2010)

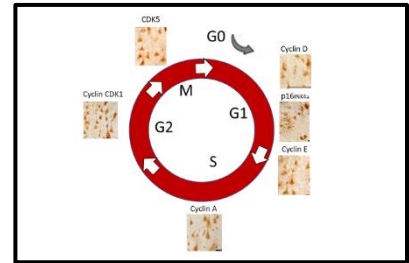


Figure 2: Cell cycle proteins inappropriately expressed in AD brain (adapted from Arendt, 2008)

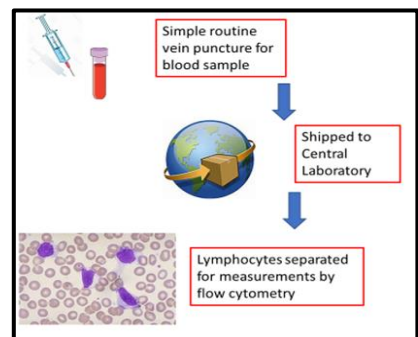


Figure 3: Sample collection

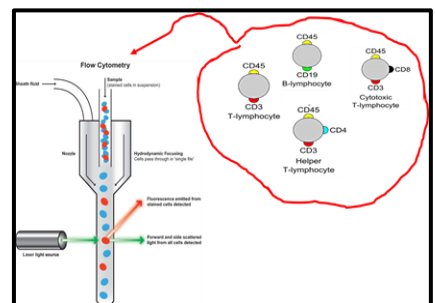


Figure 4: Sample analysis by flow cytometry post mitogenic stimulation.

LymProTest: Key Clinical Results

1. Differentiates AD from Healthy Controls as Measured by Clinical Diagnosis (Figure 5) (Stieler, et al., 2001)
2. Distinguishes AD from Parkinson’s Disease Dementia (PDD) patients and Healthy Controls. Differentiates AD and PDD with 91% positive and 92% negative agreement with clinical diagnosis (Stieler et al., 2012).
3. Differentiates AD from Healthy Controls Independent of AD Stage as Measured by Clinical Diagnosis (Figure 6) (Kirby et al, 2015).

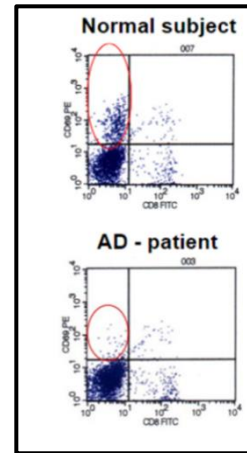


Figure 5

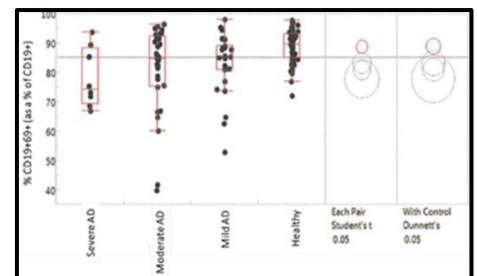


Figure 6

LymPro: The Immune – CCD Test Uniqueness

1. LymPro is the only body fluid-based test that focuses on immune cell cycle dysfunction – an independent pathological process in the neurodegeneration found in AD (Figure 7).
2. Interim analysis of an ongoing clinical validation study found a strong inverse correlation between LymPro Score and amyloid PET cSUVR. This suggests the LymPro approach may offer a means to ‘bootstrap’ to PET scan results (the antemortem diagnostic “Gold Standard”) in a cost effective, minimally invasive, and accessible manner as a convenient adjunctive diagnostic test during differential diagnosis of patients (Figure 8) (Arendt and Stieler, unpublished data, 2019).

Immune CCD		LymPro Test
	Roche Elecsys Fujirebio InnoTest	Magqu IMR Araclon Abtest Amprion
Amyloid/Tau	CSF Test	Blood Test

Figure 7: LymPro differentiation matrix

Measure	r vs PET-SUVR	p value
LymPro Score	-0.848	0.000002
MMSE Score	-0.182	0.442926

Figure 8: (Todos Medical, data on file unpublished)

Key References

1. Arendt T Chapter 8 in Handbook of Neurochemistry and Molecular Neurobiology 2008;160-213
2. Arendt T et al. Amer J Path 2010;177:15-20
3. Arendt T Presentation at 3rd Alzheimer's Focused #C4CT Concussion Awareness Summit at United Nations, July 2014
4. Kirby L et al. ADPD Conference Poster, March 2015
5. Stieler J et al. Neuroreport 2001;18:3969-3972
6. Steiler J et al. Neurobiology of Aging 2012; 33:234-341

Todos Medical Ltd: Who We Are

TODOS MEDICAL is a biotech company that is developing powerful blood-based screening diagnostics for identifying subtle, yet specific changes in the body's immune response to disease. Our unique "immune fingerprint" technologies uncover abnormal [immune system patterns that may precede clinically observed symptoms](#). Our diagnostic approach may offer the opportunity to intervene at earlier points in the disease course to improve outcomes.

Our Pipeline

Todos Breast Screens (TM-B1, TM-B2)

Todos Colon (TM-C1)

LymPro Test® for Alzheimer's Disease

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