Defining, Measuring and Tracking Disease Modification in Schizophrenia

Some Lessons from Medicine

Shitij Kapur
Institute of Psychiatry, King's College London

Outline ..

- Schizophrenia
  - Is it a single "Disease"?
  - What progresses and what does not
  - Do we have markers of progression?

- Lessons from other illnesses
  - Multiple Sclerosis
  - Rheumatoid Arthritis
  - Dementia

- What does it mean for Schizophrenia

Schizophrenia is not a Disease

It is a mental disorder
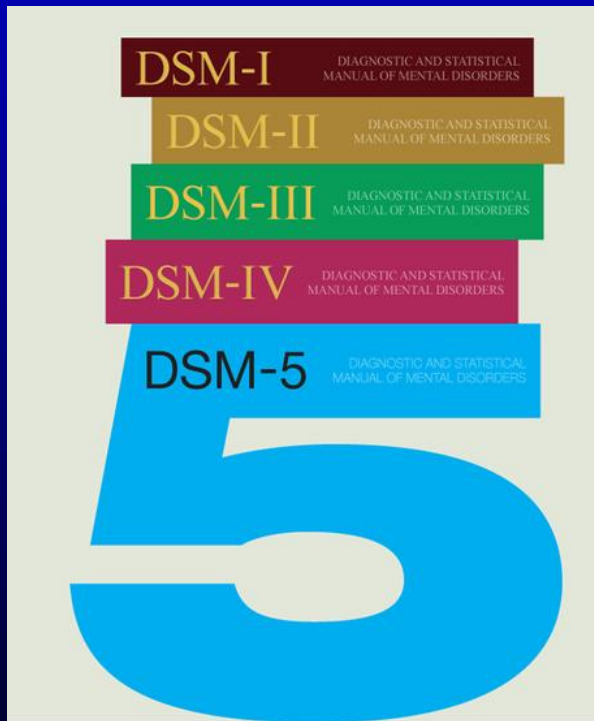
Dorland's Medical Dictionary

Disease: a definite pathological process having a characteristic set of signs and symptoms.

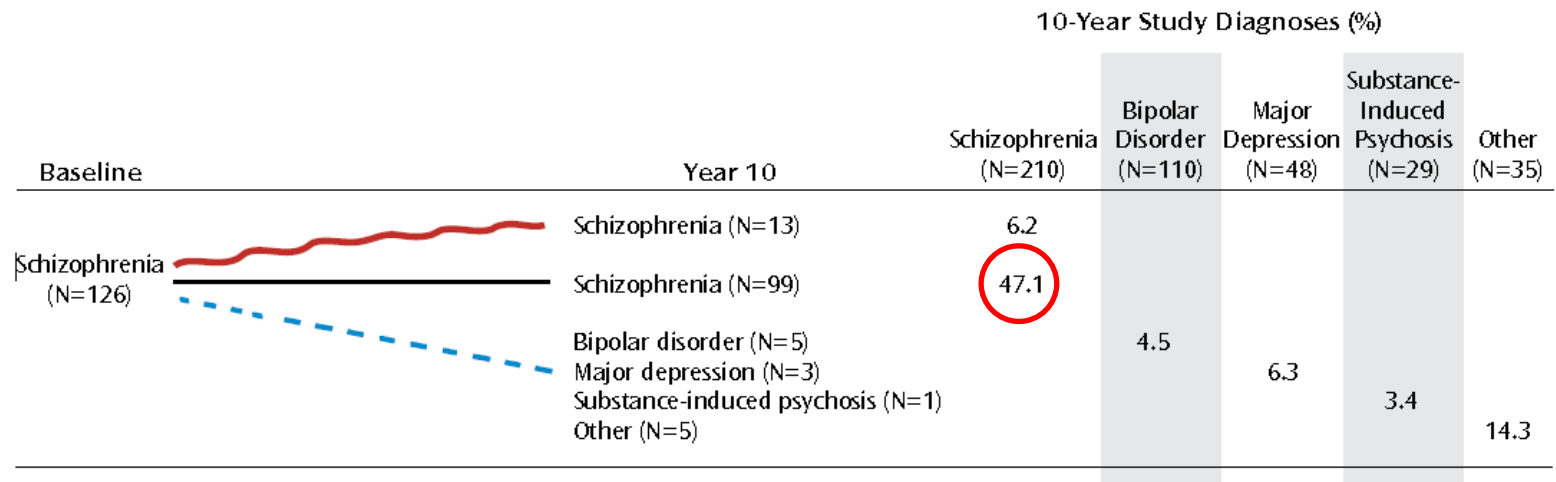**Disorder:** a derangement or abnormality of function; a morbid physical or mental state.

What is a Mental/Psychiatric Disorder? From DSM-IV to DSM-V

Dan J. Stein, Katharine A. Phillips, Derek Bolton, K.W.M Fulford, John Z. Sadler, and Kenneth S. Kendler

FIGURE 2. Pattern of Shifts in Diagnosis for 432 Study Participants With First-Admission Psychosis at Baseline Who Received Diagnoses at All Four Assessment Points[a]

Baseline	Year 10	10-Year Study Diagnoses (%)				
		Schizophrenia (N=210)	Bipolar Disorder (N=110)	Major Depression (N=48)	Substance-Induced Psychosis (N=29)	Other (N=35)
Schizophrenia (N=126)	Schizophrenia (N=13)	6.2				
	Schizophrenia (N=99)	47.1				
	Bipolar disorder (N=5)		4.5			
	Major depression (N=3)			6.3		
	Substance-induced psychosis (N=1)				3.4	
	Other (N=5)					14.3

Is there predictable decline?

- 21 studies, >5 years of follow up, ~2,000 patients, 1987 onwards

- 7-52% "Remission" (variously defined)

- 5-10% Suicide

- 34-70% with poor outcomes

- Symptoms fluctuate, negative symptoms most stable, but unclear if there is progression.

Cognition
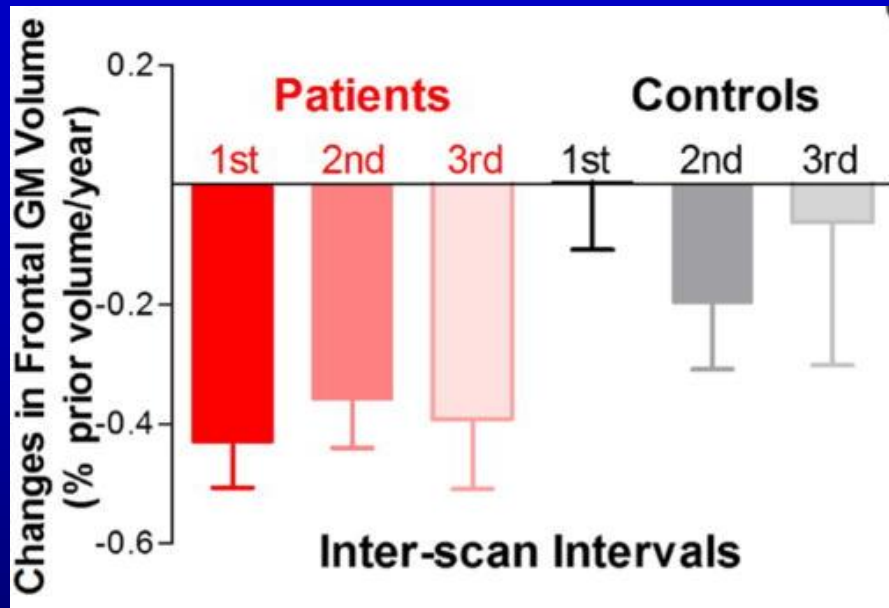
- 31 Cross-sectional and 43 Longitudinal studies

- Cross-sectional studies, suggest deterioration with time

- Longitudinal studies, suggest no change with time

- Likely effect of selection bias

Brain Structures

Progressive Brain Change in Schizophrenia: A Prospective Longitudinal Study of First-Episode Schizophrenia

Nancy C. Andreasen, Peg Nopoulos, Vincent Magnotta, Ronald Pierson, Steven Ziebell, and Beng-Choon Ho

BIOL PSYCHIATRY 2011;70:672–679
© 2011 Society of Biological Psychiatry

What Happens After the First Episode? A Review of Progressive Brain Changes in Chronically Ill Patients With Schizophrenia

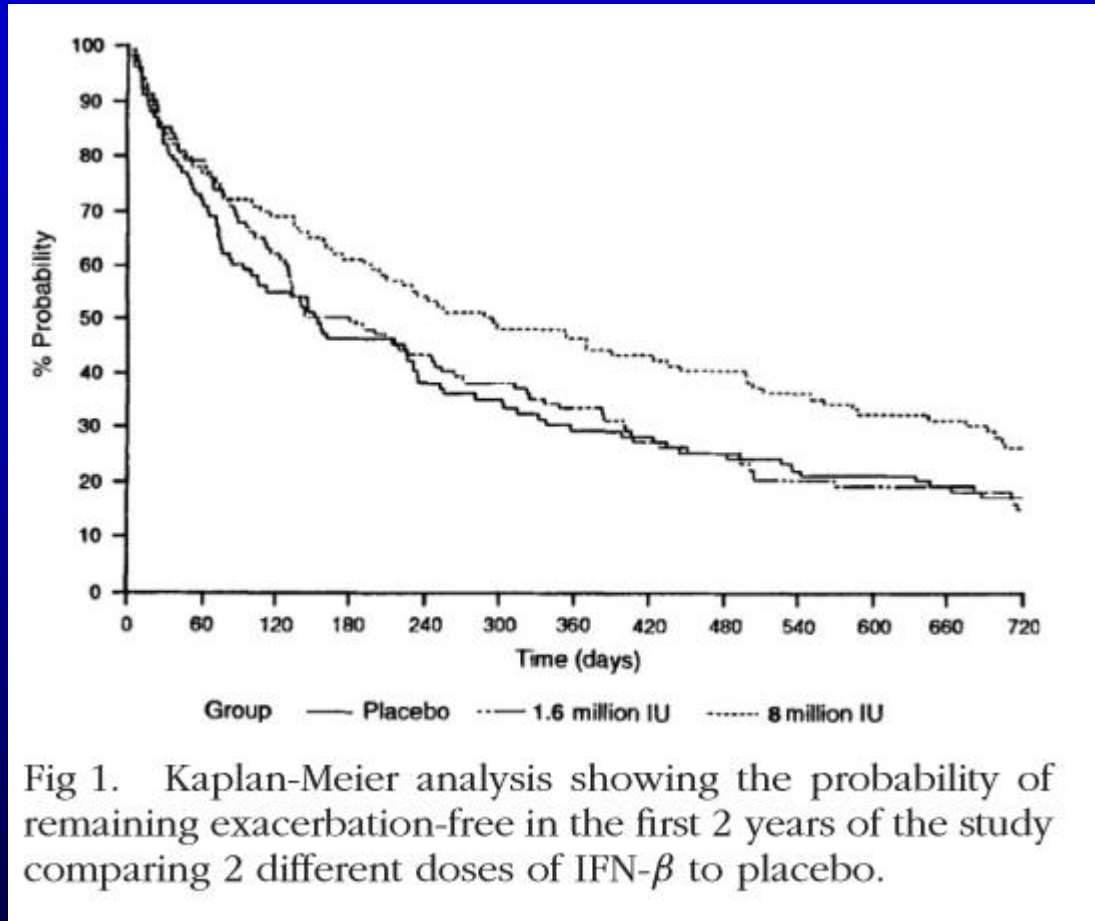Hilleke E. Hulshoff Pol[1] and René S. Kahn

Schizophrenia Bulletin vol. 34 no. 2 pp. 354–366, 2008

up to at least 20 years after their first symptoms. The extent of progressive brain tissue decrease in patients (−0.5% per year) is twice that of healthy controls (−0.2% per year).

Disease Modification

What can we learn from others?

Multiple Sclerosis

Fig 1. Kaplan-Meier analysis showing the probability of remaining exacerbation-free in the first 2 years of the study comparing 2 different doses of IFN-β to placebo.

Group —— Placebo ···— 1.6 million IU ······ 8 million IU

Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. The IFNB Multiple Sclerosis Study Group.

Multiple Sclerosis

**Table 1.** *FDA-Approved Disease-Modifying Therapies for Multiple Sclerosis.*

Medication	Dose	Route	Frequency	Approved in US	Pregnancy Category
Fingolimod (Gilenya)	0.5 mg	Oral	Daily	2010	C
Glatiramer acetate (Copaxone)	20 mg	SC	Daily	1996	B
IFNβ-1a (Avonex)	30 µg	IM	1× weekly		C
IFNβ-1b (Betaseron)	0.25 mg	SC	Every other day	1993	C
IFNβ-1b (Extavia)	0.25 mg	SC	Every other day		C
IFNβ-1a (Rebif)	22, 44 µg	SC	3× weekly	2002	C
Mitoxantrone (Novantrone)	12 mg/m^2	IV	Every 3 months	2000	D
Natalizumab (Tysabri)	300 mg	IV	Monthly	2004/2006	C

Abbreviations: IM, intramuscular; IV, intravenous; SC, subcutaneous; US, United States.
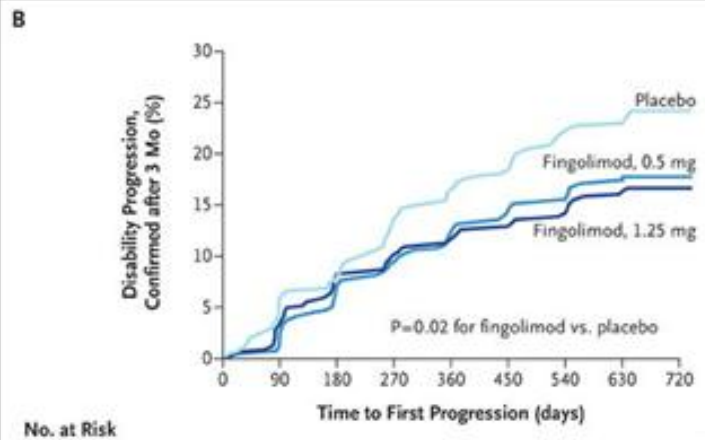
Biogen multiple sclerosis drug Tecfidera wins European approval
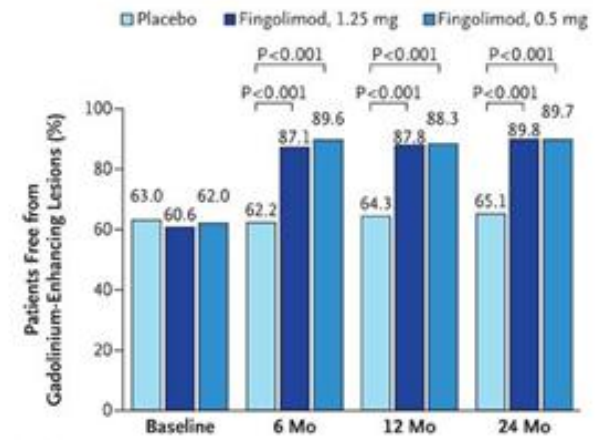
BY **BILL BERKROT**

Mon Feb 3, 2014 29pm GMT
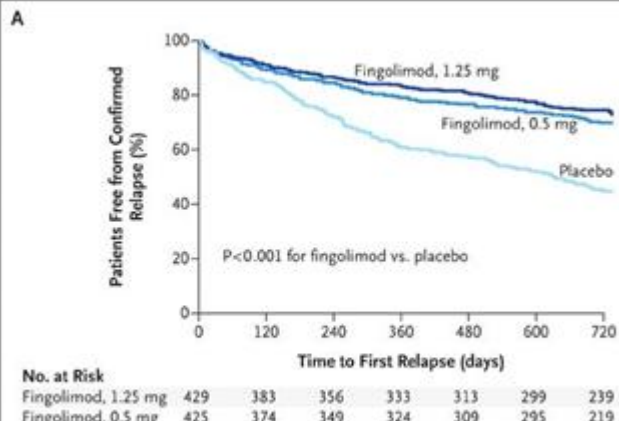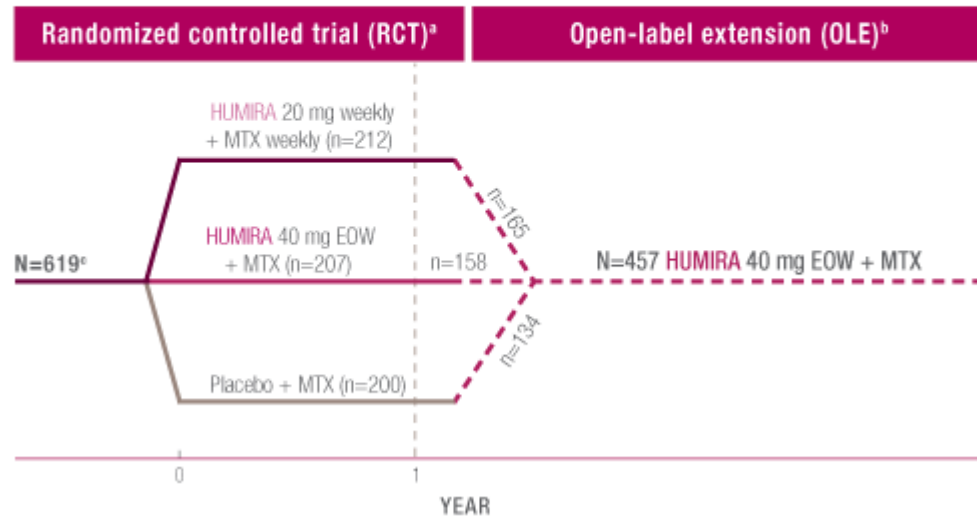
Clinical Improvement

Functional Improvement

Biomarker Improvement

Kappos L et al. N Engl J Med 2010;362:387-401
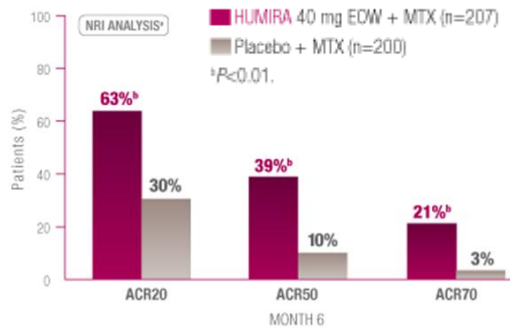
Rheumatoid Arthritis

- Symptomatic Rx with NSAIDs and Steroids

- Disease Modifying Anti-Rheumatic Drugs (DMARDs)
  - Hydroxychloroquine (Plaquenil)
  - Leflunomide (Arava)
  - Cyclosporine (Neoral)
  - Sulfasalzine (Azulfidine)
  - Methotrexate (Rheumatrex, Trexall)
  - Azathioprine (Imuran)
  - Cyclophosphamide (Cytoxan)
  - Biologics (Actemra, Cimzia, Enbrel, Humira, Simponi)

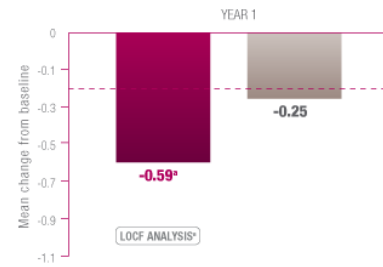DE019: Clinical study in long-standing moderate to severe RA[1-4]

DE019: Study Design[1-4]

Randomized controlled trial (RCT)[a] | Open-label extension (OLE)[b]

HUMIRA 20 mg weekly + MTX weekly (n=212)
HUMIRA 40 mg EOW + MTX (n=207)
Placebo + MTX (n=200)

N=619[c]   n=158   n=165   n=134

N=457 HUMIRA 40 mg EOW + MTX

YEAR   0   1   5

DE019 RCT: ACR Response Rates[1,2]

NRI ANALYSIS[a]
HUMIRA 40 mg EOW + MTX (n=207)
Placebo + MTX (n=200)
[b]P<0.01.

ACR20: 63%[b] / 30%
ACR50: 39%[b] / 10%
ACR70: 21%[b] / 3%

MONTH 6

ACR .. Clinical Rating Score

DE019 RCT: Improvements in HAQ-DI at 1 Year[2]

YEAR 1
Mean change from baseline
-0.59[a]   -0.25

LOCF ANALYSIS[a]

HAQ .. Patient Reported Disability Index

DE019 RCT: Mean Change in mTSS at 1 Year[2,4]

EXTRAPOLATED ANALYSIS[a]

Mean change from baseline
1.3   2.7
0.3[b]   0.1[b]

24   52
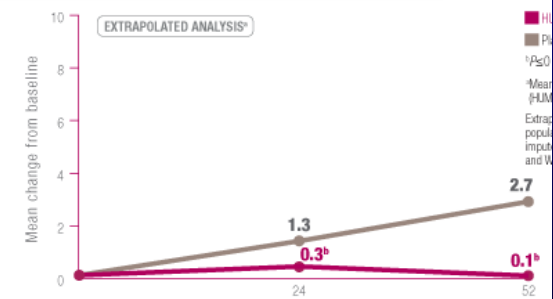
mTSS .. Radiological Erosion Score

Indications for DM drugs ..

Humira for RA

Reducing signs and symptoms, inducing major clinical response, <u>inhibiting the progression of structural damage</u>, and improving physical function in adult patients with moderately to severely active RA.

Cortisone for RA .. Per month

📍 **Sams Club**
View store details

$18.37
with discount

Humira for RA .. Per Month

📍 **Sams Club**
View store details

$5,291.51
with discount

Lessons for Schizophrenia

- The regulatory distinction between symptomatic control and "disease modification" is becoming clearer.

- Most recent DM approvals are based on a troika of:
  - Improving clinical symptoms
  - & Improvement in functional disability
  - & Related improvement in a mediating pathophysiological marker.

- In the absence of a mediating marker biomarker the burden-of-proof is higher and the pathway uncharted.

Modification Options in Schizophrenia

Define and Measure	Evidence of Progression	Biomarker	Clinical Relevance	Timeline 2-5 year study
Psychotic TRS				
Cognitive Decline				
Negative Symptoms				
Structure Brain Decline				

Is it progression or selection?

A hypothetical "modifying" Scenario

- Objective – to decrease the progression to TRS [Currently at 20% at Y2] and gray matter decline [1% at Y2] in patients treated with standard atypical antipsychotics with the addition of Marmite.

- DBRCT – patients with FE – followed for
  - Group 1: Receives TAU + Marmite +
  - Group 2: Receives TAU + Placebo +

- Outcome Variables
  - Primary – % with failure of two a
  - Secondary – Functional Outcom
  - Supportive - Decrease GM decli

- With 400 patients, followed for 2 years, y
  you have ***modified the course*** if we can
  - A) a decrease in TRS from 20% to 10%
  - B) associated with functional improvement;
  - C) change in gray matter loss from 1% to 0.6%;
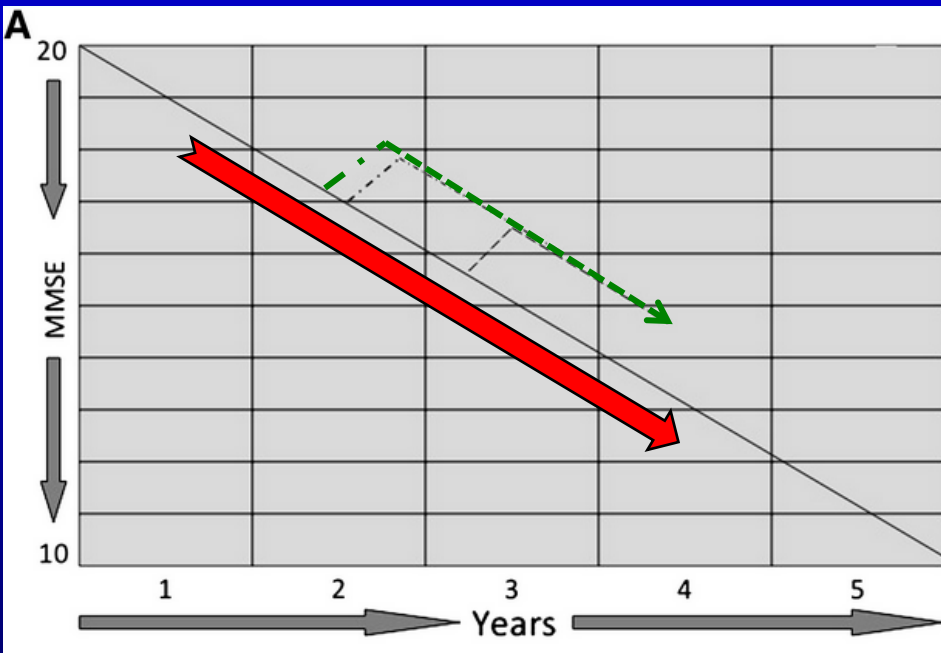 - D) that the two [GM and TRS] are correlated ($r > 0.4$).

What's needed ..

- Which patient subgroup within Schizophrenia?

- Progression of which particular symptom domain?

- What is the underlying biomarker that mediates and is modifiable?

What if there are no reliable biomarkers?

Symptomatic Treatment

Disease Modification

Defining and labeling disease-modifying treatments for Alzheimer's disease

Jeffrey L. Cummings

Alzheimer's & Dementia

Volume 5, Issue 5, September 2009, Pages 406–418