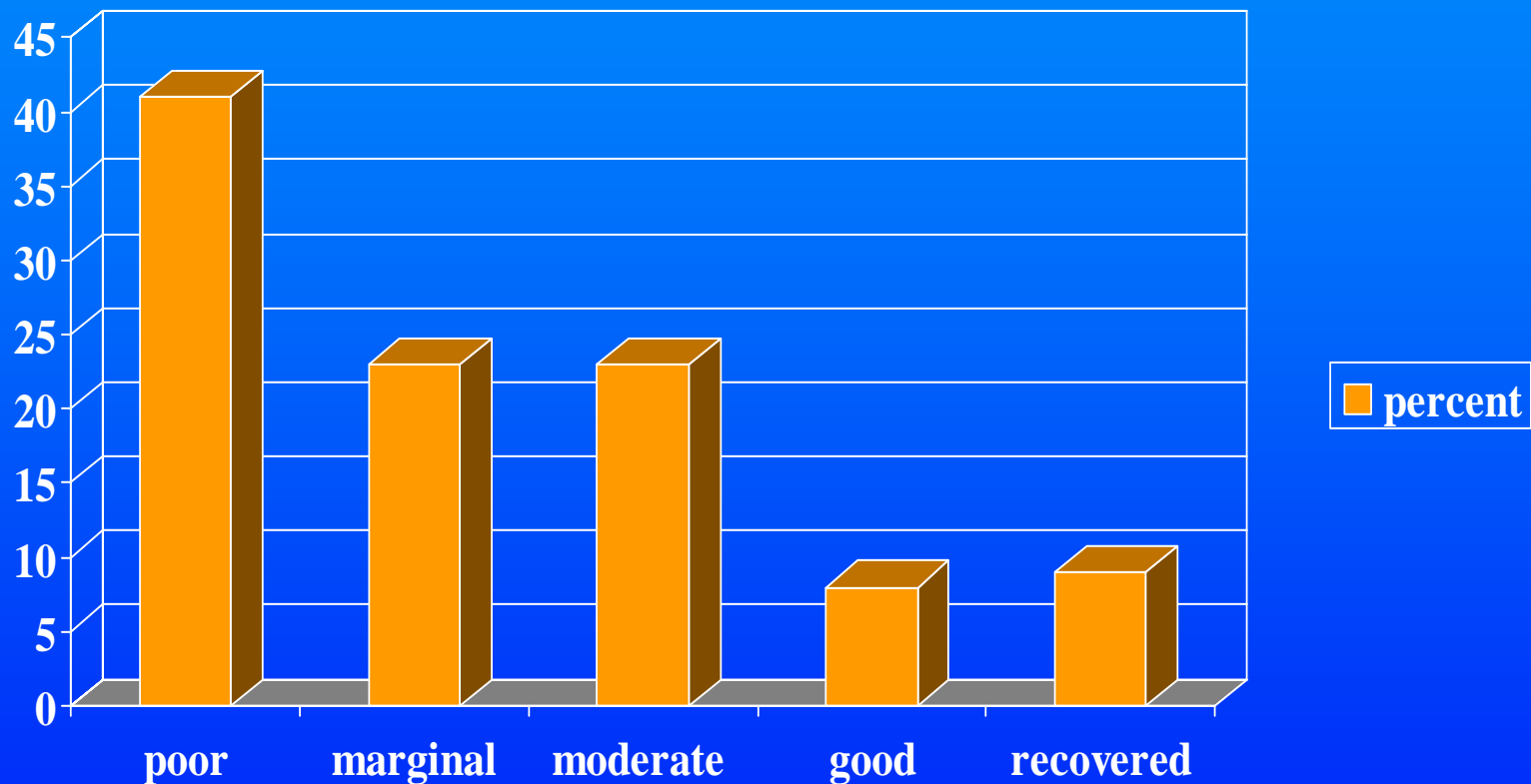


***NIMH Initiatives to Enhance Treatment
Development for Negative Symptoms in
Schizophrenia***

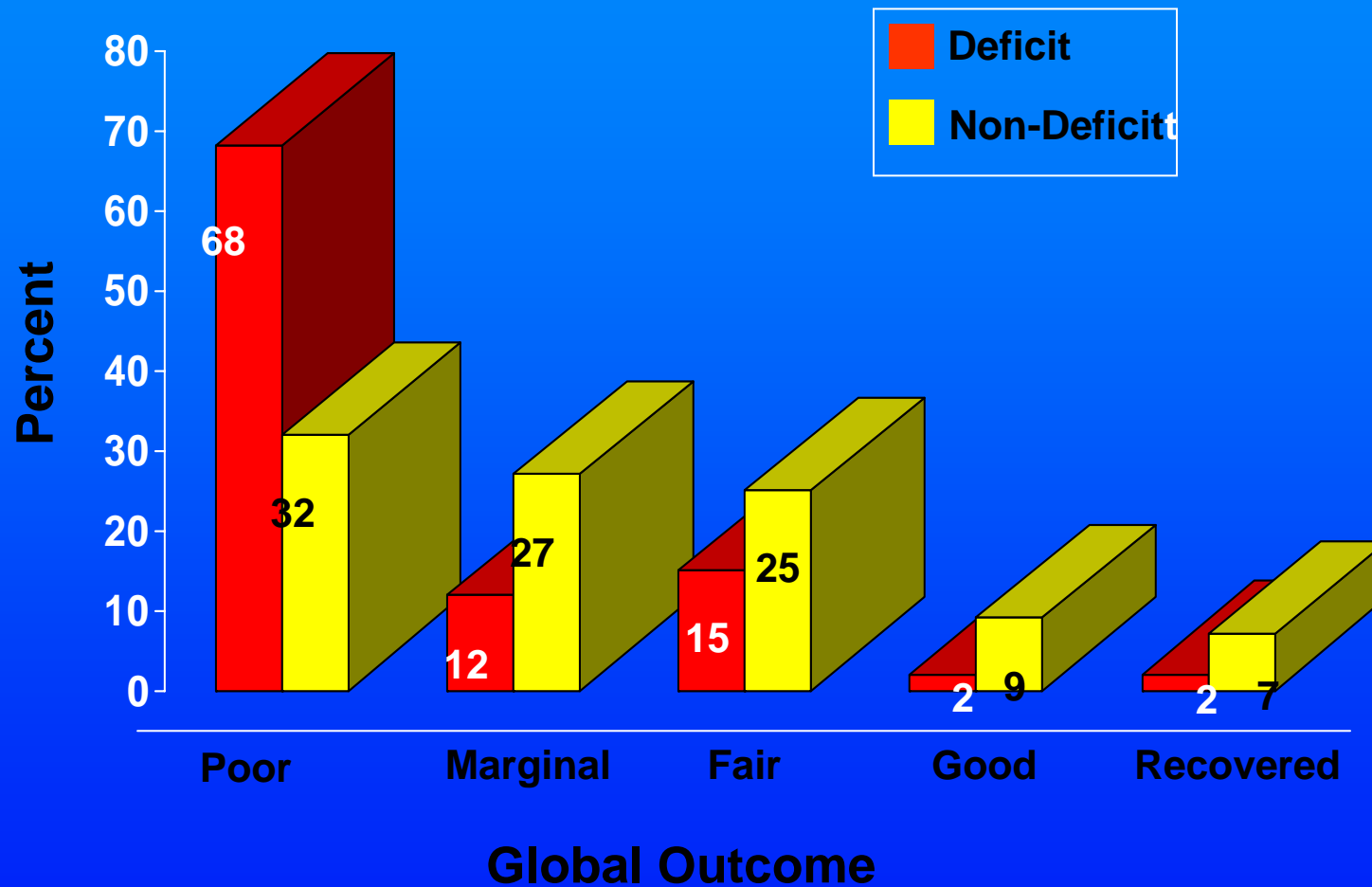
***Wayne S. Fenton, M.D.
Director, Division of Adult
Translational Research
Associate Director for Clinical
Affairs, NIMH, NIH, DHHS***



Schizophrenia: Outcome 23 years after index admission



Deficit Syndrome: Global Outcome



Negative Symptoms: Assumptions

- **Important Dimension of Schizophrenia Psychopathology.**
- **Initial enthusiasm about SGA's efficacy against negative symptoms has been tempered.**
- **No Drug Approved for Negative Symptoms of Schizophrenia.**
- **New and novel efforts at treatment development required.**

Negative Symptoms: Assumptions II

- **Clarifying clinical trial methodology required for establishing efficacy will facilitate research investment.**
- **From regulatory perspective many issues similar to those studied for cognitive deficits in MATRICS.**
- **An statement of areas of similarity and difference will be of value to treatment development efforts.**

Negative Symptoms of Schizophrenia: January 2005 - Consensus Meeting

- To review the data relating to separate domains within negative symptoms, as a prerequisite for choosing appropriate measures, and
- To initiate a process for developing or identifying evidence-based methodologies needed to establish the efficacy of treatments for negative symptoms.

NIMH/MATRICES Consensus Statement:

Academic, FDA, NIMH Participants

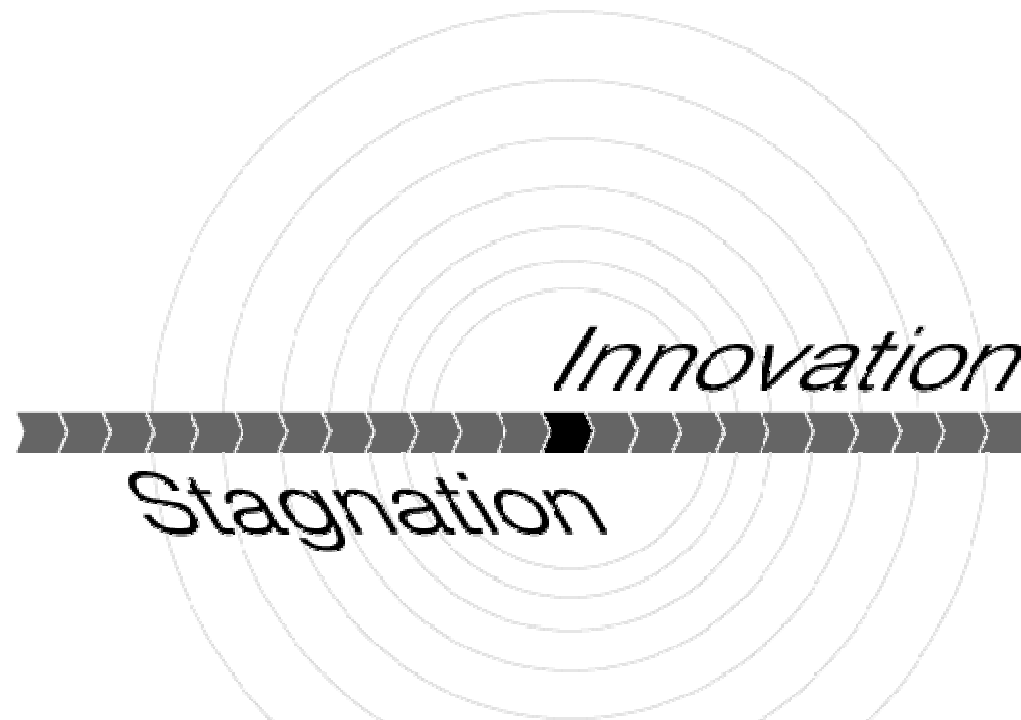
- Nancy Andreasen,
- Alan Belack
- Jack Blanchard
- Robert Buchanan
- William Carpenter
- Steve Erhart
- Wayne Fenton
- Don Goff
- James Gold
- Michael Green
- Raquel Gur
- Philip Harbey
- Robert Heinsen
- William Horan
- Dan Javitt
- Shitij Kaput
- Brian Kirkpatrick
- Ann Kring
- Thomas Laughren
- Robert Levin
- Dolores Malaspina
- Steve Marder
- Ellen Stover

January 2005 - Consensus Meeting: Areas of Agreement

- Distinct Therapeutic Indication
- Separable from Cognition
- Face Validity as Disease Manifestation
- Paradigmatic Trial Designs Definable
- Current Instruments Acceptable, but
- Re-evaluation in view of evidence of domains (expressivity/anhedonia) desirable
- Creation of New Instrument potentially useful.

Negative Symptom Activities

- **Consensus Meeting: January, 2005**
 - Academia, Government, FDA
- **NCDEU Academia/NIMH/FDA Symposium: June, 2005**
- **Expressivity and Anhedonia Workgroup Meetings: November, 2005**
- **Publication of Consensus Statement.**
 - *Schizophrenia Bulletin, Feb, 2006*
- **Presentation and Feedback for Workgroups: ISCTM, February, 2006**



**Challenge and Opportunity
on the Critical Path
to New Medical
Products**



U.S. Department of Health and Human Services
Food and Drug Administration

March 2004

Critical Path: 2006

- Press Release: February 14 2006
- Oncology Biomarker Qualification initiative
- FDA, NCI, CMS Collaborative
- FDG-PET Biomarker – Non-Hodgkin's Lymphoma

Critical Path or Development Science

- Better animal models and predictive pre-clinical screening methods.
- Biomarkers or surrogate endpoints for effectiveness: (H. pylori, CD4).
- Better paradigms for proof of concept trials in humans.
- Increase efficiency of clinical trials such as selection of patients based on genotype and Bayesian approaches to randomization.
- Methods for early prediction and detection of safety problems.
- Consensus regarding new meaningful clinical endpoints.
- Guidance for development pathway.