Is Schizophrenia an Inflammatory Disease?

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Winter CME Meeting
February 25, 2011

Disclosures

- Grant support from:
  - University of Oulu (Finland)
  - Oy H. Lundbeck, Ab
  - MCG Brain & Behavior Discovery Institute
  - MCG Immunotherapy Discovery Institute
  - MCG Intramural Scientist Training Program
- Other support from:
  - NIH (NIMH) Loan Repayment Program

Disclosures

- I will discuss “off-label” uses of the following medications in the treatment of schizophrenia:
  - Celecoxib
  - Aspirin
Objectives

- 1. To consider an alternative model that schizophrenia is not just a brain disease, but a disease of the entire body.
- 2. To discuss the evidence for immune system dysfunction in schizophrenia.
- 3. To discuss the use of immunomodulatory agents as potential adjunctive treatments in schizophrenia.
- 4. To describe current research projects and future directions.

1. WHAT IS SCHIZOPHRENIA?

[Image]

Schizophrenia:
The Four Domains of Psychopathology

- Positive Symptoms
  - Hallucinations
  - Delusions
  - Paranoia
  - Thought disorder

- Negative Symptoms
  - Affective flattening
  - Impaired speech
  - Anhedonia

- Mood Symptoms
  - Dysphoria
  - Anxiety
  - Agitation
  - Abulia

- Neurocognitive Symptoms
  - Distractibility
  - Learning difficulties
  - Memory defects
  - Abstract thinking impairment

[Image]
Standard Model of Schizophrenia

Schizophrenia
= Disease with onset in late teens/early 20's
= Psychosis (Hallucinations & Delusions)
= Dopamine dysfunction
= Brain disease

An Alternative Model

- Schizophrenia is not a psychotic disorder; it is a developmental disorder in which essentially every brain function is impaired, and psychosis is present.
- Schizophrenia is not just a brain disease; it is a disease of the entire body.
- The full risk period for schizophrenia extends throughout the lifespan.

Schizophrenia ≠ Brain Disease

- Replicated associations (increased in schizophrenia versus control subjects) of anatomical and physiological abnormalities outside the brain:
  - Maternal gestational diabetes
  - Minor physical anomalies**
  - Abnormal dermatoglyphics and nailfold venous plexus**
  - Low birth weight
  - Shorter adult height & lower BMI (prior to treatment)
  - Abnormal glucose metabolism and diabetes (prior to treatment)**
  - Autoimmune disorders**
  - IMMUNOLOGICAL ABNORMALITIES**

** Increased prevalence in 1st degree relatives
2. WHAT IS THE EVIDENCE FOR IMMUNE SYSTEM DYSFUNCTION IN SCHIZOPHRENIA?

Risk Factors for Schizophrenia

- GENETICS
Many genes of risk, each with small effect size

<table>
<thead>
<tr>
<th>Gene</th>
<th>Polymorphism</th>
<th>Race</th>
<th>Samples</th>
<th>Cases</th>
<th>Controls</th>
<th>OR</th>
<th>95% CI</th>
<th>Study</th>
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Gene x Environment Interaction

- Relative risk of Schizophrenia

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<tr>
<th>Family History of Psychosis</th>
<th>Yes</th>
<th>No</th>
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<tr>
<td>Prenatal Maternal Infection</td>
<td>Yes</td>
<td>4.60</td>
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<tr>
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<td>No</td>
<td>2.45</td>
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</table>

- If risks of prenatal infection and family history were independent, risk would be $1.36 \times 2.45 = 3.33$, but we have a risk of $4.60 \rightarrow$ synergism


BIOINFORMATICS

Genes associated w/ Schizophrenia →
2 functionally independent but integrated protein clusters

Hsu et al., Am J Psychiatry 166(8):854
Genome-Wide Association Studies (GWAS)

- 3 papers published in *Nature*, August 2009
- Found schizophrenia is associated with SNPs in the (extended) major histocompatibility complex (MHC) region on chromosome 6p21.3-22.1

Modified GWAS

- Used Gene Set Enrichment Analysis and hypergeometric test to perform a pathway-based analysis in order to detect genes’ combined effects on mediating schizophrenia.
- Found significant evidence for pathways related to inflammation/immune system
  - TGF-β signaling pathway
  - TNFR1 pathway

Risk Factors for Schizophrenia

- ENVIRONMENTAL
  - Prenatal Maternal Factors
    - Stress
    - Infection
    - Famine
  - Cytokines are a possible common pathway by which prenatal maternal “stress” may exert this risk, and may permanently alter the programming/set-point of the immune system in patients with schizophrenia.
Animal Models of Schizophrenia

- Prenatal Stress/Immune Activation
  - Lipopolysaccharide (LPS/bacterial endotoxin)
  - Poly I.C (mimics viral mRNA)
  - Mechanical/Physiologic stress

Animal Models

- BEHAVIORAL effects of prenatal maternal immune activation:
  - Spectrum of abnormalities in the offspring, including impairments in:
    - Exploratory behavior
    - Prepulse Inhibition (PPI; sensorimotor gating)
    - Memory and Learning

- IMMUNOLOGIC effects of prenatal maternal immune activation:

Animal Models

- LPS model; n=12 male rats/group, age 180 days

Romero et al., Neuropsychopharmacology, 2007;32:1791–1804
Animal Models

- Adult offspring of maternal rats exposed to LPS

Smith et al., J Neurosci, 2007;2710695–10702

AUTOIMMUNE DISORDERS IN SCHIZOPHRENIA
BROAD AREAS OF OVERLAP BETWEEN CONDITIONS

- Shared risk factors
  - Early infections
  - Genetics/Family history
- Onset in late adolescence/early adulthood
- Increased prevalence of autoantibodies
- Relapsing-remitting clinical course
- Occur comorbidly
- Alterations in blood cytokine levels

Autoimmune Disease

- All 7,704 persons in Denmark diagnosed with schizophrenia from 1981 to 1998 and their parents with a sample of matched comparison subjects and parents.
- History of any autoimmune disease was associated with a 45% risk for schizophrenia.
- Prevalence of 5 autoimmune disorders in patients with schizophrenia AND family members versus controls
  - Thyrotoxicosis
  - Interstitial cystitis
  - Celiac disease
  - Sjögren's syndrome
  - Acquired hemolytic anemia

Eaton et al., Am J Psychiatry 2006;163:521–528

(CNS) Autoimmune Disease and Cytokines: IL-6

Autoimmune Disease and Cytokines: Celiac Disease

CLINICAL TRIALS OF ANTI-INFLAMMATORIES IN SCHIZOPHRENIA: CELECOXIB (COX-2i)

Muller et al., 2002

- Patients hospitalized with acute exacerbation of psychosis randomized to Risperidone 2-6 mg/day + Celecoxib (400 mg/day) (n=25) or Placebo (n=25) for 5 weeks
  AFTER a washout period of ≥48 hrs
  - Significant ↓ PANSS total in Celecoxib versus Placebo group.

Muller et al., Am J Psychiatry 2002;159:1029–1034
Muller et al., 2004

- Cytokine data from Muller et al., 2002
- Found a significant serum sIL-2R at 5 wks
- LOWER baseline serum sTNF-αR1 was a significant predictor of response to Celecoxib (↓ PANSS total >30%)

Rappaport et al., 2005; Bresee et al., 2006

- Continuously ill patients stabilized for 12 weeks on Olanzapine or Risperidone randomized to 9 weeks of Celecoxib (400 mg/day) (n=18) or placebo (n=17)
  - NO difference in psychopathology, functional disability, or EPS
- Cytokines in Celecoxib (n=14) versus placebo (n=14) groups
  - NO change in serum sIL-2R, or in vitro stimulation of cytokine production

Akhondzadeh et al., 2007

- Patients hospitalized with acute exacerbation of psychosis randomized to 8 weeks of Risperidone 6 mg/day + Celecoxib (400 mg/day) (n=30) or Placebo (n=30) after a 1 week washout period.
- Significant improvement in PANSS total, positive, and general scores in Celecoxib group.
Caucasian patients with a diagnosis of schizophrenia or schizoaffective disorder (and illness duration less than 2 years) were randomized to Amisulpiride 200-1000 mg/day + Celecoxib (400 mg/day) (n=25) or Placebo (n=25) for 6 weeks AFTER a washout period of ≥ 48 hrs.

- Significant \( P \) PANSS negative, general, and total symptoms, as well as ↓ Clinical Global Impression scale score in Celecoxib versus Placebo group.

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CLINICAL TRIALS OF ANTI-INFLAMMATORIES IN SCHIZOPHRENIA: ASPIRIN
Adjunctive ASA in Schizophrenia

- Inpatients and Outpatients randomized to 3 months of antipsychotic (not standardized) + Aspirin (1000 mg/day) (n=33) or Placebo (n=37) after a 2 week placebo run-in
- All patients also given Pantoprazole 40 mg/day for GI prophylaxis.
- Significant improvement in PANSS total and positive scores in ASA group.
- Treatment efficacy (PANSS total) was significantly greater in patients with a lower baseline in vitro IFN-γ/IL-4 ratio

Laan et al., J Clin Psychiatry 2010;71:521-527

CYTOKINE ABNORMALITIES IN SCHIZOPHRENIA
Nunes et al., 2006
Interleukin-6 (IL-6)
- Groups matched for age, gender, BMI, albumin.
META-ANALYSIS OF CYTOKINE ABNORMALITIES IN SCHIZOPHRENIA

Brian Miller, MD, MPH
Peter Buckley, MD
Wesley Seabolt, MD
Andrew Mellor, PhD
Brian Kirkpatrick, MD
Submitted to Biological Psychiatry
In revision

Cytokine Meta-Analysis

- Existing meta-analysis (Potvin et al., 2008)

<table>
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<tr>
<th>Cytokine</th>
<th>Studies (s)</th>
<th>Substudy (e)</th>
<th>Effect</th>
<th>p</th>
<th>95% CI</th>
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<td>5</td>
<td>.110</td>
<td>.78</td>
<td>(1.679 – 8.220)</td>
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<td>IL-10</td>
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<td>.323</td>
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<td>(.235 – 7.782)</td>
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<tr>
<td>IL-6</td>
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<td>.463</td>
<td>.0001</td>
<td>(.274 – 6.802)</td>
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<td>IL-6R</td>
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<td>.013</td>
<td>.972</td>
<td>(.569 – 5.686)</td>
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<tr>
<td>TNFα</td>
<td>8</td>
<td>.209</td>
<td>.047</td>
<td>(.301 – 7.249)</td>
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<tr>
<td>IL-2</td>
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<td>.590</td>
<td>.0001</td>
<td>(.402 – 9.410)</td>
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<tr>
<td>IL-10</td>
<td>17</td>
<td>.999</td>
<td>.0001</td>
<td>(.344 – 603)</td>
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</table>


- LIMITATIONS of Potvin et al. (2008)
  - An additional 20 studies of cytokines in schizophrenia have been published since 2005.
  - There is significant heterogeneity among studies with respect to factors such as:
    1) Illness Duration
      - (i.e., first-episode vs chronic psychosis)
    2) Clinical State
      - (e.g., acutely relapsed inpatients vs stable outpatients vs treatment-resistant psychosis)
Cytokine Meta-Analysis

LIMITATIONS (Cont’d)

3) In the case of acute psychotic relapse, the timing of assays for cytokine levels
   - (i.e., within days of admission, following a period of stabilization with antipsychotic medications, or after a “washout” period with no medications)
   - Correlations between cytokine levels and psychotic symptoms have not summarized

Cytokine Meta-Analysis

LIMITATIONS (Cont’d)

- Changes in cytokine levels over time in patients treated with antipsychotics following acute relapse have not been described.
- Many individual studies do not control for factors known to influence blood cytokine levels, including: fasting, time of collection, age, race, sex, BMI, smoking, SES, cortisol, and medications.

Cytokine Meta-Analysis

Why Does Clinical Status Matter?

- Acute psychotic relapse is common and relapse prevention represents an important treatment issue in schizophrenia.
- 82% of patients had an illness relapse within 5 years after recovery from a first-episode of psychosis, and a majority had more than one relapse.
**Cytokine Meta-Analysis**

Why Does Clinical Status Matter?
- Illness relapse is associated with adverse outcomes, including increased treatment-resistant symptoms, cognitive decline, and functional disability.
- Positive findings in studies in drug-naïve patients/first-episode psychosis would support an association that is independent of antipsychotic medications.

**Cytokine Meta-Analysis**

Why Does Clinical State Matter?
- Positive findings in an acute psychotic relapse (and then normalization of levels following resolution) would support cytokine as a putative
  - Biomarker in the etiopathophysiology of acute psychotic relapse, and
  - Therapeutic target for relapse prevention in schizophrenia.

**Ganguli et al., 1997**

- N=36 patients underwent weekly clinical & immunologic assessment for 1 year
- in vitro IL-2 + anti-hippocampal IgG from the previous week significantly predicted clinical state in 3 of 7 patients who relapsed.

McAllister et al., 1995

- N=64 males underwent Haloperidol withdrawal for 2-6 weeks
  - n=30 patients relapsed within 6 weeks
- Relapse and Non-relapse with similar age, age of onset of illness, duration of illness, severity of psychosis, and haloperidol dose.
- CSF IL-2 was a significant predictor of relapse
  - Serum IL-2 also higher in relapse group (p=0.13)

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**Figure 1. Flow Chart of the Study Selection Process**

- **Search Strategy:**
  - MeSH terms and/or keywords related to inflammation or cytokine or interleukin or interferon or tumor necrosis factor
  - Search: Medline, PsycInfo, ISI
  - Manual review of reference lists and supplementary material from Potvin et al. (2008)

**Included Studies for Meta-analysis**

- n=88 studies
- n=45 potential studies for meta-analysis
- n=43 included:
  - Cytokines measured after HD 4
  - No control group
  - Clinical status not available

**Studies Included in the Meta-analysis**

- n=22: First-episode psychosis
- n=14: Antipsychotic treatment for an acute illness
- n=5: Treatment-resistant psychosis

**Blood (in vivo) Cytokine Levels**

- Increased in controls, or
- Decreased with treatment
- Increased in psychosis, or
- Increased with treatment

*p<0.05*
Cytokine Meta-Analysis: Results

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Baseline</th>
<th>p-value</th>
<th>Post-Tx</th>
<th>p-value</th>
<th>Notes</th>
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<tr>
<td>IL-6</td>
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<td>&lt; 0.001</td>
<td>↓</td>
<td>0.003</td>
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<tr>
<td>IFN-γ</td>
<td>↑</td>
<td>≤ 0.006</td>
<td>↓</td>
<td>0.12</td>
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<tr>
<td>TNF-α</td>
<td>↑</td>
<td>≤ 0.001</td>
<td>↓</td>
<td>0.15</td>
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</tr>
<tr>
<td>TGF-β</td>
<td>↑</td>
<td>≤ 0.001</td>
<td>↓</td>
<td>0.005</td>
<td></td>
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<tr>
<td>IL-4</td>
<td>↓</td>
<td>&lt; 0.001</td>
<td>↑</td>
<td>0.15</td>
<td></td>
</tr>
<tr>
<td>IL-2 (in vitro)</td>
<td>↓</td>
<td>&lt; 0.001</td>
<td>↑</td>
<td>0.04</td>
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Cytokine Meta-Analysis: Results

SIGNIFICANT CORRELATIONS

- **IL-6**
  - + correlation with baseline total psychopathology (n=2)
  - + correlation with baseline SANS (n=1)
  - ∆IL-6 + correlation with ∆ total psychopathology (n=2)
  - + correlation with duration of illness (n=3)
- No other replicated significant correlations

Cytokine Meta-Analysis: Summary

- Effect sizes similar between Acute Relapse and FEP → cytokine alterations may be independent of medications
- **IL-6**: Putative biomarker of acute psychosis
  - ↑ in Acute Relapse & FEP; ↓ following antipsychotic treatment
  - ∆IL-6 + correlation with ∆ total psychopathology
- **sIL-2R**: Putative biomarker of treatment-resistant psychosis
  - Supported by a recent longitudinal treatment study (Bresee et al., 2009).
SORTING OUT CYTOKINE ALTERATIONS IN SCHIZOPHRENIA

INFLAMMATION, THE KYNURENINE PATHWAY, AND COGNITION IN SCHIZOPHRENIA

Schizophrenia: The Four Domains of Psychopathology

Positive Symptoms
- Hallucinations
- Delusions
- Paranoia
- Thought disorder

Negative Symptoms
- Affective flattening
- Impaired speech
- Anhedonia
- Anosognosia

Mood Symptoms
- Dysphoria
- Anxiety
- Apathy
- Blunted affect

Neurocognitive Symptoms
- Distractibility
- Learning deficits
- Memory defects
- Abstract thinking impairment
Schizophrenia and Cognition

- Cognitive impairment
  - A common and important predictor of overall function in schizophrenia
  - Deficits persist despite treatment with antipsychotic medications
  - Hypofunction of the N-methyl-D-aspartate (NMDA) receptor has been implicated in the pathophysiology of positive and cognitive symptoms of schizophrenia

Schizophrenia and Cognition

- Cytokines in the periphery are able to cross the blood brain barrier and exert effects in the brain, including activation of astrocytes.
- Recent meta-analysis found significantly increased serum levels of S100β, a marker of astrocyte activation and blood brain barrier dysfunction, in patients with schizophrenia (Schroeter et al., 2009).

Schizophrenia and Cognition

- Indoleamine 2,3-dioxygenase (IDO), the rate-limiting enzyme in tryptophan degradation, is also expressed in astrocytes and microglial cells.
- IDO induction results in increased production of kynurenine, which in astrocytes is converted to kynurenic acid (KYN-A).
Schizophrenia and Cognition

- Kynurenic acid (KYN-A) is the only known endogenous NMDA receptor antagonist
- In schizophrenia, ↑ KYN-A has been found in
  - Plasma (Ravikumar et al., 2000)
  - CSF (Nilsson et al., 2005)
  - Postmortem brain tissue (Schwarcz et al., 2003)
- Behavioral studies in rats and mice have found causal associations between ↑ cortical KYN-A levels and cognitive impairments similar to those seen in schizophrenia

- ↑ IDO activity is also reported in patients with schizophrenia (Barry et al., 2009).
- Cytokines influence IDO activity
  - Induced by IFN-γ & TNF-α (both ↑ in Schizophrenia)
  - Inhibited by IL-4 and IL-10 (both ↓ in Schizophrenia)

Conceptual Model
Specific Aim

- We will test the hypothesis that patients with an acute relapse of schizophrenia (and related disorders) (n=30) have increased blood levels of IL-6, IL-17, S100β, and kynurenic acid, increased blood IDO activity than
  - i) stable outpatients with schizophrenia (n=30),
  - ii) their first-degree unaffected relatives (n=30), and
  - iii) healthy controls (n=30)

Hypotheses (Cont’d)

- These associations are not confounded by age, sex, race/ethnicity, IQ, BMI, socioeconomic status, alcohol use, smoking, cortisol concentration, or psychotropic medications.
- In all subject groups, higher blood IL-6 and kynurenic acid levels are associated with greater cognitive impairment, and the effect will be greater in schizophrenia.
Infections in Schizophrenia

- Patients with schizophrenia have increased mortality from infectious diseases:
  - 8.35-fold increased risk of death from pneumonia (Brown et al., 2010)
  - A meta-analysis found a 4.56-fold increased risk of death from all infectious diseases (Saha et al., 2007).

Infections in Schizophrenia

- Common clinical knowledge that infections may precipitate psychotic symptoms in certain conditions (e.g., UTIs in elderly patients with dementia).
- 13 of 79 (16%) consecutive admissions to a geriatric psychiatry unit had unrecognized infections on admission (Woo et al., 2003)
  - 7 patients (9%) with UTIs, all of whom had psychosis as a clinical symptom

Infections in Schizophrenia

- In my clinical training, I observed that many patients with an acute exacerbation of psychosis had evidence of an active infection on hospital admission.
  - Most commonly (females) with a UTI.
  - Treatment of the underlying infection was often associated with improvement in psychotic symptoms, even in the absence of antipsychotic medication changes (including patients adherent with medications).
Specific Aim

- Measure prevalence of UTI in subjects with:
  - Acute psychotic relapse (n=57)
    - Data obtained from retrospective chart review
  - Stable outpatients with schizophrenia (n=40)
  - Health controls (n=40)

PRELIMINARY RESULTS

- n=13 (23%) of acutely relapsed patients have cystitis on admission by urinalysis!

Cytokines as a Mechanistic Link?

- There is evidence for ↑ IL-1β, IL-6, and IL-8 in the urine, but not in the blood, of patients with cystitis.
- IL-6 and IL-8 levels are ↑ in both the urine and blood of patients with acute pyelonephritis (upper UTI).
- Blood levels of IL-6 and IL-8 may be ↑ in cystitis, but were below the detection limit of the cytokine assays available at that time.

4. Future Research
Future Studies

- Secondary analysis of blood samples from the PROACTIVE study
  - 8-site randomized trial of long-acting injectable antipsychotic (Risperidone Const) versus oral antipsychotics for relapse prevention.
  - N=43 patients with data on acute relapse and blood draws every 6-8 weeks for 30 months
- Serial cytokine levels as a temporal predictor of relapse

Potential Future Studies

- Simultaneous measurement of peripheral blood and CSF cytokine levels in schizophrenia.
- Trial of a "statin" as an adjunct for improved cognition in schizophrenia.
- Trial of adjunctive Tociluzimab (anti-IL-6R antibody) for patients with an acute relapse of psychosis.
- Trial of an adjunctive anti-inflammatory agent or *relapse prevention* in schizophrenia.
- Trial of an adjunctive antibiotic for relapse prevention in patients with a history of cystitis.

Future Studies: Big Picture

- There appears to be a subset of patients with schizophrenia for whom blood cytokine levels may be a biomarker of:
  - Illness relapse
- Characterization of cytokine levels represents an advancement towards personalized medicine, and may identify potential therapeutic targets for relapse prevention, psychotic symptoms, and cognitive impairment.
Acknowledgements

- Georgia Health Sciences University
  - Peter Buckley, MD
  - Andrew Mellor, PhD
  - Diane Addis, BS
  - Chelsea Bodenheimer, MD
  - Krystle Crittenden, DO
  - Adriana Foster, MD
  - Dave Hill, PhD
  - Lei Huang, PhD
  - Christina Lynn, MD
  - Texas A&M and Scott and White
  - Brian Kinpatrick, MD, MSPH

- Texas A&M and Scott and White
  - Dawn Montoya, BS, CCRC
  - Rebecca Nichols, BS, CCRC
  - Dale Sebastian, MBBS
  - Simon Sebastian, MD
  - Sarita Sharma, MD
  - Edna Stirewalt, BS, CCRC
  - Lynn Tyson, MD
  - Scott Van Sant, MD
  - Christy Wise, BA

- Kelly, Ethan, Jacob, Drew Miller

Thank you! Questions?
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