Agenda

Organization and Administration

7:30 - 8:00  Continental Breakfast
8:00 - 8:05  Welcome             Russell Swerdlow, MD
8:05 - 8:10  Message from Vice Chancellor for Research    Richard Barohn, MD
8:10 - 8:50  Infrastructure, Theme and Progress         Russell Swerdlow, MD

Metabolism-Focused Research: From Bench to Bedside to Community

8:50 - 9:55  Molecular and Cellular Studies in AD
Overview and Infrastructure                        Elias Michaelis, MD, PhD
Targeting Mitochondria as a Potential Therapeutic Strategy for Alzheimer’s Disease Shidu Yan, MD
Dark Amyloid and Mitochondrial Dysfunction          Michael Wolfe, PhD*
Mitochondria and Alzheimer’s Disease                 Heather Wilkins, PhD*
What Memories Are Made Of                           Kausik Si, PhD*

9:55 - 10:10  Break

10:10 - 11:10  Clinical and Translational Research in AD
Overview and Infrastructure                        Jeffrey Burns, MD, MS
Cells-to-Systems Metabolism                          Jill Morris, PhD*
Vascular Contributions to Brain Health                Sandra Billinger, PT, PhD*
Nutrition and Brain Health                           Debra Sullivan, PhD, RD*

11:10 - 11:55  Empowering Community Through Science and Care
Overview and Infrastructure                        Eric Vidoni, PT, PhD*
Becoming an Independent Researcher in Latino AD Disparities Jaime Perales Puchalt, PhD
MyAlliance for Cognitive Health: Shifting the Point of Care Michelle Niedens, LSCSW

11:55 - 12:00  Closing Remarks                       Russell Swerdlow, MD
*KU ADC Pilot awardees
Virtual Site Visit

October 19, 2018
Message from Senator Jerry Moran
Message from Richard Barohn, MD
Overview:
KU ADC Infrastructure, Theme, and Progress

Russell Swerdlow, MD
PI, P30 AG035982
Year 7 Overall Metrics

- Investigators: 150
  - 96 members, 54 users
  - 102 KU, 48 non-KU
- Projects Supported: 111
- Portfolio Value
  - $17.5 million in year 7
  - $65.8 million worth of grants
- Manuscripts Supported: 72

### 111 Total Projects Supported

<table>
<thead>
<tr>
<th>Direct Support</th>
<th>Indirect Support</th>
<th>Total Supported</th>
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<tbody>
<tr>
<td>39 Federal (5 are training awards)</td>
<td>29 Non-Federal</td>
<td>78</td>
</tr>
<tr>
<td>19 Industry</td>
<td>24 Unfunded</td>
<td>53</td>
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</tbody>
</table>

[kualzheimer.org](http://kualzheimer.org)
Aim 1: Advance AD and Brain Aging Research

• Promote research into AD energy metabolism dysfunction
• Develop field-driving capabilities and initiatives
• Support innovative research into AD and related topics
Energy Metabolism Dysfunction: Causes, Consequences, Manipulations

- Genetics
  - mtDNA associations
  - mtDNA-nDNA interactions
- Ketogenic Diet Clinical Study
- Oxaloacetate Clinical Study
- S-equol Clinical Study
- Ongoing (APEX) and New (IGNITE, rrAD) Exercise Trials
- SGLT2 Study

<table>
<thead>
<tr>
<th>Haplogroup</th>
<th>Group</th>
<th>Frequency</th>
<th>Fisher's Exact P</th>
<th>AD APOE4 Frequency</th>
<th>CN APOE4 Frequency</th>
<th>Fisher's Exact P</th>
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<tbody>
<tr>
<td>H</td>
<td>AD</td>
<td>63/144=43.8%</td>
<td>0.755</td>
<td>38/62=61.3%</td>
<td>30/110=27.3%</td>
<td>0.0001</td>
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<tr>
<td></td>
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<td>119/262=45.4%</td>
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<tr>
<td>J</td>
<td>AD</td>
<td>23/144=16.0%</td>
<td><strong>0.031</strong></td>
<td>15/23=65.2%</td>
<td>5/22=22.7%</td>
<td><strong>0.007</strong></td>
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<td>22/262=8.4%</td>
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</tr>
<tr>
<td>T</td>
<td>AD</td>
<td>11/144=7.6%</td>
<td>0.712</td>
<td>10/11=90.9%</td>
<td>5/24=20.8%</td>
<td><strong>0.0001</strong></td>
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<tr>
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<td>Control</td>
<td>24/262=9.2%</td>
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</tr>
<tr>
<td>U</td>
<td>AD</td>
<td>20/144=13.9%</td>
<td>0.185</td>
<td>11/19=57.9%</td>
<td>7/22=31.8%</td>
<td><strong>0.122</strong></td>
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<tr>
<td>K</td>
<td>AD</td>
<td>8/144=5.6%</td>
<td>0.138</td>
<td>3/8=37.5%</td>
<td>7/24=29.2%</td>
<td><strong>0.681</strong></td>
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<tr>
<td>UK</td>
<td>AD</td>
<td>28/144=19.4%</td>
<td>1.000</td>
<td>14/27=51.9</td>
<td>14/46=30.4</td>
<td><strong>0.085</strong></td>
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<td>52/262=19.8%</td>
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</tbody>
</table>
Field Driving Capabilities

- Biomarker Disclosure
- New Biomarkers
  - N-acetyl aspartate (MRS)
  - Glutathione (MRS)
  - Mito Protein Nitration
  - Platelet Cytochrome Oxidase
  - Annexin Binding
- Bioenergetic Medicine Drug Development
- Exercise Prescription
- Recruitment Approaches
- REDCap
- Service Delivery
Enhance and Support Innovative Research

- IPSCs
- TBI-AD Connection
- “Dark Amyloid”
- O-GlycNAcylation
- Mitophagy
- Molecular Basis of Memory
- Microfluidic Biomarker Assays
- Neurovascular Control in AD
Aim 2: Serve as a Midwestern Hub for AD Research, Care, and Education

• Bring together investigators
• Provide a rich training environment
• Provide well-characterized research participants and biospecimens
Aim 2: Serve as a Midwestern Hub for AD Research, Care, and Education

- Bring together investigators
- Training environment
- Participants and biospecimens

<table>
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<tr>
<th>Resources</th>
<th>Notes</th>
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<tr>
<td>Blood Biospecimens</td>
<td>Q4 years; stored at KUMC BRCF</td>
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<tr>
<td>Genetic Data</td>
<td>mtDNA especially</td>
</tr>
<tr>
<td>Clinical Data</td>
<td>ADC-initiated and project-initiated</td>
</tr>
<tr>
<td>Imaging</td>
<td>ADC-initiated and project-initiated</td>
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<tr>
<td>Expertise</td>
<td>Study/Protocol development</td>
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<tr>
<td>Technical Support</td>
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<tr>
<td>Clinical Trial Infrastructure</td>
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<tr>
<td>Pilot Support</td>
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<tr>
<td>Cybrid Cell Lines</td>
<td></td>
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<tr>
<td>IPSCs</td>
<td></td>
</tr>
<tr>
<td>Brain</td>
<td></td>
</tr>
<tr>
<td>CSF</td>
<td>Project-driven; changing to ADC-initiated</td>
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</table>
Aim 3: Enhance the ADC Network

• Contribute to the national ADC network
• Foster new lines of research
Aim 3: Enhance the ADC Network

- National Network
- New Lines of Research

Novel Lines of Research
- Biomarker Development
- Drug Development
- Fitness/Lifestyle Intervention
- Genetics
- Metabolism/Mitochondria
- Prevention

New Infrastructure Approaches
- Data Capture
- Information Dissemination
- Participant Recruitment
- Service Delivery

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## Administrative Core

<table>
<thead>
<tr>
<th>Primary Affiliation</th>
<th>Department</th>
<th>Number</th>
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<td>Pathology</td>
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<tr>
<td>Biochemistry</td>
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<tr>
<td>Microbiology</td>
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<td>Neurology</td>
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<tr>
<td>Pharmacology</td>
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<td>KU-Lawrence Chemistry</td>
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<td>Pharm-Tox</td>
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<tr>
<td>Bioengineering</td>
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<td>KU-Wichita Neuropsychology</td>
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<tr>
<td>Stowers Neuroscience</td>
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<tr>
<td>KCU Biochemistry</td>
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</table>

### Interaction with other KU Programs/Cores
- CTSA
- KU Cancer Center (P30CA168524)/BRCF
- Kidney Institute (P30DK106912)
- KUMC Institute for Neurologic Discoveries
- Higuchi Biosciences Center
- KU Hospital
- Landon Center on Aging
- Center for Physical Activity and Weight Management
- Heartland Center for Mitochondrial Medicine

### What Others Seek Us Out For
- Investigator-Initiated Multicenter Trials (especially exercise)
- Recruitment Expertise
- Imaging Expertise (human and animal)
- Metabolism/Mitochondrial Expertise
- Metabolism/Mitochondrial Technical Abilities (including biomarkers)
- mtDNA/cybrids
- REDCap Data Capture
Clinical Core

• Formal “research” cohort of ~400 active participants
  • Skewed toward CN due to prevention interests
  • Rarely used for intervention studies

• Maintains clinical study infrastructure
  • Clinical Trials Unit
  • Study Coordinators
  • Regulatory support staff
  • 43 supported studies in year 7 (19 federally funded)
Data Management and Statistics Core

• Electronic Data Capture
  Boston University
  Columbia University
  Emory University
  Indiana University
  New York University
  Northwestern University
  Oregon Health and Science University
  Stanford University
  University of California, Irvine
  University of California, San Francisco
  University of Florida
  University of Michigan
  University of Pennsylvania
  University of Southern California
  University of Washington
  University of Wisconsin
  Wake Forest University
  Washington University in St. Louis
  Yale University
Outreach and Recruitment Core

• Lifestyle Enhancement for Alzheimer’s Prevention (LEAP)
  • Community based, culturally tailored education

• LEAP Physician Engagement
  • Stimulates referrals across regional health systems
Neuropathology Core

• Cadaveric dural and fibroblast-derived iPSCs
REC: Training Program Structure

- Undergraduate Programs
- WSU URM Program

- Summer Med Student and TL1
- Health Professions Programs
- Graduate IGKBP Program
- Woodyard Fellowship
- Neuro & Rehab T32
- Health Psychology Program

- Neurology Residency
- Post-doc fellow recruitment
- Woodyard Fellowship
- Health Professions Graduates
- IGKBP Graduates

- Departmental Recruitment
- KL2 program

Developing Scholar Internship
  - Structured Projects under member investigators
  - Research observation
  - Data collection
  - CReW meetings

Graduate and Medical Student Training Program
  - Semi-Independent or
  - Structured Projects under member investigators
  - CReW/Node meetings

Kansas Dementia Fellowships
  - Independent Research under members
  - Clinical Experiences
  - Didactic & Practical Training
  - CReW/Node Meetings
  - Scholars Club

Junior Faculty
  - Independent Research
  - Research Nodes
  - CReW/Node Meetings
  - Scholars Club

Research-minded medical and graduate students

Research post-doc fellows and medical residents

Neuroscientists
Neurologists
Gerontologists
# Year 7 Training Grant Applications

<table>
<thead>
<tr>
<th>Mentee</th>
<th>Mentor</th>
<th>Grant Type</th>
<th>Status</th>
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<tr>
<td>Wilkins, Heather</td>
<td>Swerdlow</td>
<td>K99-R00</td>
<td>Funded</td>
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<tr>
<td>Koppel, Scott</td>
<td>Swerdlow</td>
<td>F30</td>
<td>Funded</td>
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<tr>
<td>Gupta, Aditi</td>
<td>Burns/Brooks</td>
<td>K23</td>
<td>Funded</td>
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<tr>
<td>Devos, Hannes</td>
<td>Burns/Brooks</td>
<td>K01</td>
<td>Pending</td>
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<tr>
<td>Szabo-Reed, Amanda</td>
<td>Burns/Brooks</td>
<td>KL2</td>
<td>Pending</td>
</tr>
<tr>
<td>Perales, Jaime</td>
<td>Swerdlow/Vidoni</td>
<td>NIA Diversity Supplement; K01</td>
<td>Supplement Funded, K01 Pending</td>
</tr>
</tbody>
</table>
Neuroimaging Core

• Investigator-Initiated Multisite Trial Support
  • Harmonization of imaging protocols
  • Development and deployment of novel sequences

• MRIs on 305 clinical cohort participants
  • Repeat scans on 120 participants

• Amyloid PET on 305
  • Repeat scans on 75
Mitochondrial Genomics and Metabolism Core

• Complete mtDNA sequences for all Clinical Cohort participants
• Study consultation/design
  • Heavily utilized within and beyond KU
  • Year 2018: 15 of 21 pilot project applications would use the Core
• Biomarker and drug development
Molecular & Cellular Investigations: The Mitochondrial Genomics and Metabolism (MGM) Core

KU ADC Kansas City and Lawrence
E. Michaelis, R. Swerdlow, M. Michaelis
D. Hui, H. Wilkins
MGM Core: Not mandated — A Core designed to take advantage of the scientific environment of the KU ADC

*Scientific themes of the KU ADC:* Metabolism and Bioenergetics deficits in AD: Molecular/Cellular to Clinical Approaches
Cellular & Genetic Focus on Mitochondrial Function and Structure in LOAD

Rationale

• Decreases in activity of oxidative phosphorylation (OXPHOS)--**Systemic**
• Increases in reactive oxygen (ROS) / nitrogen species (RNS)
• ROS leading to mitochondrial DNA (mtDNA) mutations or protein modifications
• History of maternal LOAD— greater risk than paternal history of LOAD
• Possible inherited mutations in mtDNA— single nucleotide variants (SNVs) in LOAD
Mission of the MGM Core

Provide investigators with information and the tools to conduct metabolism, genomic, and proteomic analyses of mitochondria and attract investigators interested in relating such measures to mitochondrial bioenergetics in aging and AD
Goals of the MGM Core

a) Trans-Mitochondrial Cybrid Cell generation from AD/MCI/NL subjects
b) Mitochondrial bioenergetics measurements
c) Mitochondrial protein modification analyses
d) Exploratory bioenergetics drug testing (cells, animal models, humans)
e) mtDNA Next Generation Sequencing (NGS) and post-sequencing analyses on the entire cohort of the KU ADC
Developing cell models of AD

*Link between mitochondrial function and AD-related synaptic deficiencies and neuronal damage*

- Generated 100 hybrid cell lines by inserting platelet mitochondria into ρ0 SH-SY5Y neuroblastoma cells (*Cybrids*—Drs. Swerdlow, Wilkins)
- Cybrids derived from mitochondria of AD, MCI, and NL individuals
- Also from amyloid (+) and amyloid (-), cognitively normal individuals
- Shared cybrids with investigators of the ADC and others in the US and other countries
Cell models and mitochondrial metabolism measurements

Cybrids used to probe:
• effectiveness of ROS scavengers in reversing effects of Aβ on neuronal structure and function — (Dr. Yan)
• relationship between systemic metabolism, neuroimaging measures, and mitochondrial function in 40 cybrid lines — (Dr. Morris)

Planned experiments to probe:
• effectiveness of activators of mitochondrial bioenergetics — (Dr. Forrest, Pharmaceutical Chemist)
• relationship between various forms of Aβ peptides and metabolism (Dr. Wolfe)
Mitochondrial Genomics—mtDNA NGS

- Amplified, sequenced, curated, and analyzed mtDNA from 144 AD, 262 NL, and 37 MCI
- 19 SNVs only 1 SNV over-represented in NL
- AD-related SNVs: 4 non-synonymous mutations in OXPHOS enzyme subunits
- 3 SNVs in mt tRNA or rRNA

AD (16.7%) NL (8.4)  
AD (16%) NL  
AD (5%) NL (1%) *  
AD (19%) NL (9.5) *  
AD (16%) NL (8.4)
Effect of MGM Core on Scientists at KU

- Year 2018:
  - 15 of 21 Pilot Project applications would use the MGM Core
  - 3 of 5 pilot projects approved use the MGM Core
- Years 2016/2017:
  - 3 of 4 projects funded were MGM Core related

*Presentations from four individuals who have received support to explore new areas of research in molecular and cellular aspect of AD*
Heather Wilkins, PhD

- Postdoctoral fellow in the KU Alzheimer’s Disease Center
- Expert in cell bioenergetics, cybrid cell studies, and the development of induced pluripotent cells into neuronal forms for the study of the effects of Aβ and tau on neuronal metabolism
- Recipient of a K99/R00 award from the NIA
Mitochondria and Alzheimer’s Disease

Heather Wilkins, PhD
Postdoctoral Fellow
University of Kansas Alzheimer’s Disease Center
How do mitochondria affect Alzheimer’s Disease Pathology?

Several prior studies link mitochondrial function/bioenergetics to amyloid precursor protein (APP) processing and amyloid beta production

Gasparini et al. 1999.. Neurosci Letters.
Leuner et al. 2012. Antioxidants and Redox Sig.


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Mitochondrial Membrane Potential
Mitochondrial Membrane Potential

Control  FCCP  Oligomycin

Supported by the KU ADC and MGM core
Mitochondrial Membrane Potential and APP/Amyloid

Supported by the KU ADC and MGM core

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Induced Pluripotent Stem Cell Derived Neurons

ADC25, Non-demented

ADC37, Alzheimer’s disease

Supported by the KU ADC, MGM core, neuropathology core, and NIA K99 AG056600

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How does APOE influence mitochondria?

APOE ε4 carriers have reduced platelet mitochondrial cytochrome oxidase (COX) Vmax

(Willkins et al. Redox Biology. 2017)

• WHY?

ETC complexes=ATP or energy production
APOE Genotype and Blood Mitochondrial Biomarkers

![Graph showing COX Vmax (msec⁻¹/mg protein) for Non-Carriers and All Carriers.](chart)

Supported by a KU ADC pilot award

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APOE Genotype and Blood Mitochondrial Biomarkers

![Graph showing Annexin V percentages for Non-Carriers and All Carriers]

- Non-Carriers: n=16
- All Carriers: n=19

Annexin V (%)

Supported by a KU ADC pilot award
## Sex and Blood Mitochondrial Biomarkers

<table>
<thead>
<tr>
<th>Mean (SEM)</th>
<th>Male</th>
<th>Female</th>
<th>p value</th>
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</thead>
<tbody>
<tr>
<td>Annexin V (%)</td>
<td>29.5 (1.9)</td>
<td>28.9 (2.1)</td>
<td>0.84</td>
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<tr>
<td>JC1</td>
<td>3 (.17)</td>
<td>3.65 (.25)</td>
<td>0.04</td>
</tr>
<tr>
<td>n</td>
<td>18</td>
<td>17</td>
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</tbody>
</table>

Supported by a KU ADC pilot award
Future

- Mitochondrial membrane potential and secretase enzyme function
- Understand the effects of APOE ε4 on mitochondrial function
- Develop new mitochondrial and bioenergetic biomarkers
- Transition to an independent Alzheimer’s Disease Scientific Career
Clinical and Translational: Overview and Infrastructure

Jeffrey M. Burns, MD, MS
Co-Director and Clinical Core Leader
Edward H. Hashinger Professor of Neurology
“Product” and “Process” Innovation Drives Impact

Metabolism-Based Research

Lifestyle Interventions

Recruitment: Team and Processes

Community Care Network

SYNERGY
Year 7: Clinical Core Productivity

• 43 total studies supported
  • Data (15 studies), Biospecimens (10 studies), Participants (11 studies)
• 13 NIH multi-site collaborations
  • NACC, ADGC, ADNI, ADCS and ACTC
  • 3 Multi-site R01s
  • 5 NIH multi-site studies
    • ADNI3, A4, LEARN, ASPREE, and EXERT
• 23 externally funded grant awards
  (19 federal awards)

• Dramatic growth supported by
  • Clinical Cohort
  • Development of Other Cohorts
    • APEX (R01)
    • Registry (n > 7000)
  • Infrastructure creation: physical and team-based
    • CTSA
    • Trial teams (drug and exercise)
    • Recruitment
Clinical Cohort

Active cohort ~ 400 participants

ASSESSMENTS

- Phlebotomy (every 4 years)
- MRI (every 2 years)

Mitochondrial genome

Other

- Accelerometry (every 2 years)
- VO2peak / Cardiorespiratory Fitness
- Neurovascular

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Clinical Cohort

ASSESSMENTS

- Phlebotomy (every 4 years)
- MRI (every 2 years)

Mitochondrial genome

Other

- Accelerometry (every 2 years)
- VO2peak / Cardiorespiratory Fitness
- Neurovascular
Clinical Cohort

Accomplishments
• Efficient processes
  • REDCap electronic data capture
    • Time to finalization 57 days (vs. 120 days nationally)
  • Excellent retention
    • 11% discontinuation rate
    • Missed follow up 13% (vs. 20% nationally)
• Autopsy Program
  • 63% consent rate
  • 59% autopsy rate (44 of 75 all time deaths)
• Imaging submitted to NACC
  • MRIs n=252
  • Amyloid PET n=294

Active cohort ~ 400 participants
Clinical Cohort  = “Innovation and Discovery Cohort”

- Cohort not sufficient for our growing intervention studies
- Cohort “contaminated” by interventions

**Re-defined Purpose:** Natural history study to support longitudinal observational studies (biomarkers, imaging, risk factors, etc)
Clinical Cohort = “Innovation and Discovery Cohort”

### Studies Leveraging the Clinical Cohort

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<th>Study</th>
<th>Sponsor</th>
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<tbody>
<tr>
<td>Tech for Dementia Care (Williams)</td>
<td>R01</td>
<td>41</td>
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<tr>
<td>Functional Regulation (Johnson)</td>
<td>Internal Funds</td>
<td>61</td>
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<tr>
<td>Group exercise via iPad in AD (Vidoni/Ptomey)</td>
<td>ADC Pilot</td>
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<tr>
<td>Energetics and Cognition (Morris)</td>
<td>R00</td>
<td>52</td>
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<tr>
<td>TrACR (Billinger)</td>
<td>ADC Pilot &amp; Am. Heart Assoc</td>
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<td>Ketogenic Diet Feasibility (Sullivan)</td>
<td>ADC Pilot</td>
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<tr>
<td>Aging, AD and Mitochondrial Function (Morris)</td>
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<td>Neurovascular and Exercise Response (Vidoni)</td>
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<tr>
<td>KSU COBRE Neuroplasticity</td>
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<tr>
<td>Neurophysiology in Preclinical AD (Devos)</td>
<td>KU ADC Pilot / K01</td>
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<tr>
<td>Neurovascular Impairment in Aging and AD</td>
<td>R01</td>
<td>Pending</td>
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</tbody>
</table>

Active cohort ~ 400 participants
Amyloid PET Cohort

- APEX R01 Exercise Trial
- N=304 Cognitively Normal (CDR 0 and neuropsych)
  - 28% elevated amyloid (n=86 vs. n=218 nonelevated)
- Projects supported
  - Billinger – Neurovascular program
  - Morris – Insulin resistance studies
  - Taylor / Sullivan – Diet studies
  - K awards (Morris and Devos)
  - F32 award (Perdomo)
Amyloid PET Cohort

Research Registry

• Enroll online, paper, phone
• Demographic, PMH, medications, cognitive issues
• Recruit for study opportunities
  • Clinical Cohort
  • Trials
  • Others (Genematch)
Leveraging Infrastructure to Scale Up

Integrated with CTSA and CTSA Research Unit
Creating Infrastructure to Scale Up

Support Teams

- Physical Health Intervention Team
- Clinical Trial Unit
- Clinical Cohort
- Recruitment
- Neuropsych
- Med Monitoring
Clinical Trial Unit

Program Leader
Jeffrey Burns, MD, MS

Administrative Director
Becky Boothwell

Assistant Director
Aiden Bondurant

AD Trials Lead Coordinator
Annette Becker

AD Trials Lead Coordinator
Melissa Dodd

Prevention Trials Lead Coordinator
Aiden Bondurant

Coordinator
Heidi Anderson

Coordiator
Erin Schwartz

Coordinator
Leah Lambert

Coordinator
Tim Ross

Coordinator
Jane Ledesma

Research Assistants
Rachel Starr

Will Mitchell

James Pollow

Jenee Grant

### Study

<table>
<thead>
<tr>
<th>Study</th>
<th>Sponsor</th>
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<tbody>
<tr>
<td><strong>Multi-Site Trials</strong></td>
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<td>ENGAGE</td>
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<td>M15-566 Anti-Tau Ab</td>
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<td>Generation 1</td>
<td>Novartis</td>
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<td>Generation 2</td>
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<td>GRADUATE II</td>
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<td><strong>Investigator-Initiated Trials</strong></td>
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<td>Oxaloacetate</td>
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<td>S-Equolin in AD</td>
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<td>Dapa in AD</td>
<td>Astra-Zeneca</td>
<td>Start up</td>
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<td><strong>Closed</strong></td>
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<td>ASPREE</td>
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<td>MK-8931</td>
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<td>NEUROTROPE</td>
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<td>EARLY</td>
<td>Janssen</td>
<td>1</td>
</tr>
<tr>
<td>DAYBREAK</td>
<td>Eli Lilly</td>
<td>3</td>
</tr>
</tbody>
</table>
Clinical Trial Unit

Program Leader
Jeffrey Burns, MD, MS

Administrative Director
Becky Bothwell

Assistant Director
Aiden Bondurant

AD Trials Lead Coordinator
Annette Becker

AD Trials Lead Coordinator
Melissa Dodd

Prevention Trials Lead Coordinator
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Heidi Anderson

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Leah Lambert

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Tim Ross

Coordinator
Jane Ledesma

Research Assistants
Rachel Starr
Will Mitchell
James Pollard
Jeanie Grant

Annual Study Enrollments

<table>
<thead>
<tr>
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kualzheimer.org
Physical Health Intervention Team

Current Exercise Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Sponsor</th>
<th>Enrollment</th>
<th>Goal</th>
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<tbody>
<tr>
<td>APEX</td>
<td>R01</td>
<td>120</td>
<td>125</td>
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<tr>
<td>rrAD</td>
<td>R01</td>
<td>73</td>
<td>160</td>
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<tr>
<td>IGNITE</td>
<td>R01</td>
<td>55</td>
<td>213</td>
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<td>EXERT</td>
<td>ADCS</td>
<td>5</td>
<td>10</td>
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<tr>
<td>LEAP! Rx</td>
<td>R01</td>
<td>2</td>
<td>220</td>
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</tbody>
</table>
Metabolic Approaches

**Investigator Initiated Drug Trials**
- Oxalaoacetate for AD (Alzheimer’s Association)
- S-Equol for AD (Ausio Pharmaceuticals)
- Pilot RCT of Dapagliflozin in AD (Astra Zeneca)

**Exercise / Diet**
- Diet Studies
  - NICE Study (R01)
  - Ketogenic Diet for AD
- Exercise Trials (4 R01s supported)
Exercise in the Fight Against AD

Our studies suggest
1. Exercise has brain benefits, even at low doses
2. Exercise may slow AD (disease modification)
3. Optimal target is to increase CR Fitness

But, we still need rigorous scientific data to
1. Definitively prove brain benefits
2. Understand magnitude of effects
   • What kind and how much is best?
3. Understand mechanisms
Translating biomedical research findings into everyday strategies for Alzheimer’s prevention and brain health.

Evidence-based lifestyle program for risk reduction
- LEAP! book: Brainpower Blueprint
- Interactive education programs in community

LEAP! accomplishments
- Rural outreach program established in Emporia, KS
- LEAP! Rx program funded by NIH
  - Goal: to scale program nationally
Poised for Growth: New Studies

Funded in 2017 and 2018
- R21: Thyfault / Morris – Skeletal Muscle Abnormalities in AD
- R01: Ptomey – Remote Delivery of Weight Loss in older IDD
- R01: Burns – Prescribing Smart Aging (LEAP! Rx)
- K23: Gupta – Cognitive Impairment in Renal Disease
- P20 COBRE (KSU) – Cognitive Approaches to Neuroplasticity
- Diversity Supplement: Perales – Cognitive Impairment in Latinos
- K99: Wilkins – iPSC studies in AD
- KL2: Szabo-Reed – Executive Control and Exercise Adherence
- R01: Billinger – Neurovascular Impairment in Aging and AD
- R01: Sullivan – Mediterranean Diet in Aging
- IIT (Astra Zeneca): Burns/Swerdlow – Dapa in AD

New Industry / NIH Multi-site
- ADNI 3
- AbbVie
- EARLY
- Generation 2
- Pegasus (Amylyx)
- Graduate (Roche)

Pending Grants
- R01: Lee – Glutathione MRS in Exercise
- R01: Swerdlow – Ketogenic Diet in AD
- R01 Siengsukon – Insomnia and Cognitive Impairment
- K01 Devos – Neurophysiology in Preclinical AD
- K01 Szabo-Reed – Correlates of Exercise Adherence
- R01 Swerdlow – Mito DNA / Haplogroup J and AD
4350 Shawnee Mission Parkway
Fairway, KS 66205
913-588-0555
kualzheimer.org
Jill Morris, PhD

- Assistant Professor of Neurology
- Director of the KU ADC Pilot Grant Program
- Chair of Biospecimen Committee
- Researching energy metabolism and cognitive decline
Cells-to-systems metabolism

Jill K. Morris, PhD
Assistant Professor
Department of Neurology
Growing as a translational researcher
Growing as a translational researcher

Translational projects

Humans, cells, tissues
Exercise, Neuroimaging, Molecular bioenergetics

Key seed support: KU ADC

Human subjects
Insulin resistance & AD

Cell and animal models
Insulin resistance & PD

Meaningful collaborations across disciplines

R00 (NIA) 2018

K99 (NIA) 2015
R21 (NIA) 2016

Post Doc (Neurology)
KU ADC pilot 2012

F32 (NIA) 2013

BA (Biochemistry) F31 (NINDS) PhD (Physiology)
2006 2009 2011
Increased neuropathology and disease progression in prediabetic subjects

### Cognitively Normal

Prediabetes increases regional cerebral amyloid

### MCI

<table>
<thead>
<tr>
<th>Measure</th>
<th>Timepoint</th>
<th>Normoglycemia</th>
<th>Impaired Glycemia</th>
<th>p-value (2yr Δ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCI to AD converters</td>
<td>Baseline</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2yr Δ</td>
<td>32.7% (16.4%/yr)</td>
<td>47.9% (24.0%/yr)</td>
<td>0.015</td>
</tr>
<tr>
<td>CDR-SB</td>
<td>Baseline</td>
<td>1.56 (0.86)</td>
<td>1.61 (0.84)</td>
<td>0.044</td>
</tr>
<tr>
<td></td>
<td>2yr Δ</td>
<td>1.35 (1.9)</td>
<td>1.88 (1.9)</td>
<td></td>
</tr>
<tr>
<td>Global Cognition</td>
<td>Baseline</td>
<td>-0.615 (0.55)</td>
<td>-0.761 (0.61)</td>
<td>0.019</td>
</tr>
<tr>
<td></td>
<td>2yr Δ</td>
<td>-0.193 (0.55)</td>
<td>-0.366 (0.58)</td>
<td></td>
</tr>
<tr>
<td>Whole Brain Volume</td>
<td>Baseline</td>
<td>0.677 (0.027)</td>
<td>0.672 (0.02)</td>
<td>0.024</td>
</tr>
<tr>
<td></td>
<td>2yr Δ</td>
<td>-0.012 (0.007)</td>
<td>-0.0152 (0.009)</td>
<td></td>
</tr>
<tr>
<td>Hippocampal Volume</td>
<td>Baseline</td>
<td>0.655 (0.90)</td>
<td>0.642 (0.08)</td>
<td>0.439</td>
</tr>
<tr>
<td></td>
<td>2yr Δ</td>
<td>-0.0152 (-.016)</td>
<td>-0.0194 (0.019)</td>
<td></td>
</tr>
</tbody>
</table>

Prediabetes increases disease progression in MCI

*Morris et. al. 2016, NBA; Morris et. al. 2014, NBA*
Peripheral IR tracks with decreased brain volume

Morris et al 2014
AD subjects exhibit skeletal muscle insulin resistance
Exercise in Aging and AD

- **BAP** *(Brain Aging Project: 2006-2008)*
  - Longitudinal observational study, ND and AD
- **TEAM** *(Trial of Exercise on Aging and Memory: 2008-2013)*
  - Exercise trial, cognitively healthy elderly
- **ADEPT** *(Alzheimer’s Disease Exercise Program Trial: 2010-2015)*
  - Exercise trial, probable AD
- **APEX** *(Alzheimer’s Prevention through Exercise: 2014-ongoing)*
  - Exercise trial, cognitively healthy elderly “at risk” for AD
TEAM (Cognitively healthy elderly)
# ADEPT (Alzheimer’s Disease)

<table>
<thead>
<tr>
<th></th>
<th>Timepoint</th>
<th>Stretching and Toning Control</th>
<th>Aerobic Exercise</th>
<th>Arm by Timepoint Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Memory Composite</strong></td>
<td>Baseline</td>
<td>-2.8 (1.4)</td>
<td>-2.5 (1.4)</td>
<td>$X^2 = 0.82 (2), p = 0.66$</td>
</tr>
<tr>
<td></td>
<td>Week 13</td>
<td>-2.8 (1.5)</td>
<td>-2.3 (1.5)</td>
<td></td>
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<tr>
<td></td>
<td>Week 26</td>
<td>-2.7 (1.7)</td>
<td>-2.3 (1.7)</td>
<td></td>
</tr>
<tr>
<td><strong>Executive Function Composite</strong></td>
<td>Baseline</td>
<td>-1.34 (0.85)</td>
<td>-1.12 (0.82)</td>
<td>$X^2 = 2.6(2), p = 0.27$</td>
</tr>
<tr>
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<td>Week 13</td>
<td>-1.25 (0.94)</td>
<td>-1.09 (0.86)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Week 26</td>
<td>-1.33 (0.97)</td>
<td>-1.20 (0.90)</td>
<td></td>
</tr>
<tr>
<td><strong>Disability Assessment for Dementia</strong></td>
<td>Baseline</td>
<td>91.2 (8.0)</td>
<td>88.0 (12.3)</td>
<td>$X^2 = 8.2(2), p = 0.02$</td>
</tr>
<tr>
<td></td>
<td>Week 13</td>
<td>89.5 (12.8)</td>
<td>89.8 (12.5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Week 26</td>
<td>86.7 (13.3)</td>
<td>89.5 (13.7)</td>
<td></td>
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<tr>
<td><strong>Cornell Scale for Depression in Dementia</strong></td>
<td>Baseline</td>
<td>7.4 (3.8)</td>
<td>8.6 (5.1)</td>
<td>$X^2 = 1.3(2), p = 0.51$</td>
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<tr>
<td></td>
<td>Week 13</td>
<td>8.1 (4.4)</td>
<td>8.4 (4.6)</td>
<td></td>
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<tr>
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<td>Week 26</td>
<td>7.8 (4.4)</td>
<td>7.8 (5.2)</td>
<td></td>
</tr>
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</table>

Mean (standard deviation) unless otherwise noted.

doi:10.1371/journal.pone.0170547.t002
AD subjects: fitness and memory/brain benefit are positively linked

Overall:
- Individuals who do improve fitness with AEx improve memory and hippocampal volume
- AD subjects: more variable response to exercise
  - Modest fitness gain (3% AD vs 8% in ND)

Do differences in cellular energy metabolism play a role?
Next step: assess tissue mitochondrial function in early disease (MCI)

Aging and Disease Mitochondria (R21 AG056062)
Multidisciplinary collaboration: Dr. John Thyfault, Dr. Morris and Dr. Swerdlow

- Non-brain targets may affect AD susceptibility via lifestyle, genetics, or other factors
- Muscle mitochondrial function has not been measured in MCI or AD
- Fitness is partially dependent on muscle mitochondrial content and respiratory function, and declines in AD
MCI subjects exhibit impaired mitochondrial function in muscle

Muscle Biopsy Procedure

Muscle fiber bundle

Palmitoyl-Carnitine

<table>
<thead>
<tr>
<th>Condition</th>
<th>Normal Control (n=22)</th>
<th>MCI (n=12)</th>
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<tbody>
<tr>
<td>Basal</td>
<td>0.0299</td>
<td>0.0150</td>
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<tr>
<td>ADP</td>
<td>0.0329</td>
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<td>Succinate</td>
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<td>Cyto c</td>
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<tr>
<td>Uncoupled</td>
<td>0.0329</td>
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</table>
No difference in activity levels
Future work

• Cross sectional mitochondrial function + relationship with fitness
  • $H_2O_2$ emission, mitochondrial and respiratory chain content, transcriptional regulation of biogenesis, morphology, -omics, etc
  • Cells to systems relationships

• Exercise trials: bioenergetics, metabolism, vascular, neuroimaging
  • Mechanisms
  • Acute exercise
  • Better trial design
Thank you to our team!!!!!

Morris Laboratory
Casey John, MS
Ashwini Kamat

KU ADC
Anne Arthur, ARNP
Ashley Thompson
Kayla Meyer
Angela Van Sciver
Ian Weidling
Arianna Christian, MS
Briana Bright
Mark McClellan

Students
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Nicole Burns
Alexis Aiman

KUMC Collaborators
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Eric Vidoni, PhD
John Thyfault, PhD
Russell Swerdlow, MD
Colin McCain, PhD
Heather Wilkins, PhD
Xiaowen Wang, PhD
Jonathan Mahnken, PhD
Sandra Billinger, PhD
Matthew Taylor, PhD
Paige Geiger, PhD
William Brooks, PhD

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Sean Adams, PhD (UAMS)
Brian Piccolo, PhD (UAMS)
Ozioma Okonkwo, PhD (Wisconsin)
Jakob Haus (Michigan)

CTSU nursing support

FUNDING
NIA R00 AG050490
NIA R21 AG056062
NIA P30 AG035982

Research Volunteers
Sandra Billinger, PT, PhD

- Associate Professor in the Department of Physical Therapy and Rehabilitation Science
- Director of the Research in Exercise and Cardiovascular Health (REACH) lab
- Investigating vascular contributions to brain aging and neurologic conditions
Vascular Contributions to Brain Health

Sandra A Billinger, PhD, PT, FAHA
Associate Professor
KU Medical Center
Pathway to AD Research

2002-2014

2014-2015
Pathway to AD Research

- 2015: KU ADC Pilot Grant
- 2016-2018: American Heart Association Grant in Aid
- 2017: Co-I on 2 Multi-site RCTs rrAD, R01AG04979, IGNITE, R01AG053952
- September 2018: Patent 18KU028M-02
- September 2018: First R01 (Multi-PI grant)
- Model-based Cerebrovascular Markers Extracted from Hemodynamic Data for Diagnosing MCI or AD and Predicting Disease Progression (USC, UTSW, KUMC)

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Brain Blood Flow Velocity to Exercise
Brain Blood Flow Velocity Response to Exercise

Age and Brain Blood Flow Velocity Response to Exercise

Ward, 2018; AJP-Heart and Circulatory Physiology
A Brain “Exercise Stress Test”
Trial for Assessing Cerebrovascular Regulation (TrACR) in Older Adults

APEX (Burns: R01AG043962)
- Well characterized (cognitive, physical function)
- PET scan for Amyloid status (non-elevated/elevated)
- Neuroimaging core for MRI
  - White matter lesions (WML)

Billinger Lab (Billinger, KU ADC Pilot, 2015; AHA Grant-in Aid, 2016)
- Vascular risk
  - ASCVD score
  - Peripheral vascular measures (BP, Flow-mediated dilation, FMD)
  - Cerebrovascular regulation, CVR
Blunted CVR to Exercise with Increased Amyloid Load

Sisante, et al, J Cerebral Blood Flow and Metabolism, 2017
Endothelial Function Diminished with Increased Amyloid Load
Forward Momentum in AD Research

2015
KU ADC Pilot Grant

2016-2018
American Heart Association Grant in Aid

2017
Co-I on 2 Multi-site RCTs rrAD, R01AG04979 IGNITE, R01AG053952

September 2018
Patent 18KU028M-02
Model-based Cerebrovascular Markers Extracted from Hemodynamic Data for Diagnosing MCI or AD and Predicting Disease Progression (USC, UTSW, KUMC)

2018
First R01 (Multi-PI grant)

September 2018
Model-based Cerebrovascular Markers Extracted from Hemodynamic Data for Diagnosing MCI or AD and Predicting Disease Progression

- Multi-site trial (USC, Vasilis Marmarelis; KU, Billinger; UTSW, Rhong Zhang)
- Leveraging existing infrastructure with P30/ADC
  - OR Core, Clinical Core, NeuroImaging Core
- Baseline Measures for 25 ND, 25 MCI, 25 Early AD
  - Neuropsych testing
  - PET Scan (Amyloid-Florbetaben)
  - WML
  - Vascular Hemodynamics (TCD, MAP, NIRS)
- Repeated yearly except PET (3-year follow up)
Forward Momentum in AD Research

- **American Heart Association Grant in Aid**
- Co-I on 2 Multi-site RCTs rrAD, R01AG04979 IGNITE, R01AG053952
- September 2018
- Patent 18KU028M-02
- First R01 (Multi-PI grant)
- Paving pathway for future scientists
- Model-based Cerebrovascular Markers Extracted from Hemodynamic Data for Diagnosing MCI or AD and Predicting Disease Progression (USC, UTSW, KUMC)
Future AD Scientists

Post doctoral Fellows

Sophy Perdomo, PhD
University of Pittsburgh
Vascular Health
Arterial Stiffness
KU ADC REC (1 year fellowship)
F32 grant, December 2018

Andrea Freemyer, PhD
KU Medical Center
Neuroscience
Neuroplasticity
Cognition

PhD Student

Emily Witte, MS
Brain Health
Acute Exercise
Debra Sullivan, PhD, RD

• Chair of the Department of Dietetics and Nutrition
• Midwest Dairy Council Professor in Clinical Nutrition
• Understanding the impact of nutrition and weight loss on disease processes
Nutrition and Brain Health

Debra K. Sullivan, PhD, RD
Chair & Midwest Dairy Endowed Professor of Clinical Nutrition
Department of Dietetics and Nutrition
Nutrition at KU ADC

• ~2008
  • Neuroimaging Core
    • In-Young Choi, PhD
    • Phil Lee, PhD
  • Measure cerebral glutathione
    • Potent antioxidant
  • Added food frequency questionnaire
    • Exploratory study
Dairy intake is associated with brain glutathione concentration in older adults$^{1-3}$

In-Young Choi, Phil Lee, Douglas R Denney, Kendra Spaeth, Olivia Nast, Lauren Ptomey, Alexandra K Roth, Jo Ann Lierman, and Debra K Sullivan

• Observational Study
• Funding: Dairy Research, Inc.
• n = 60 participants
• Cognitively normal older adults
Cerebral Glutathione Levels and Dairy Intake

<table>
<thead>
<tr>
<th></th>
<th>GSH-frontal $r_s$</th>
<th>GSH-parietal $r_s$</th>
<th>GSH-fronto-parietal $r_s$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dairy (servings/d)</td>
<td>0.394</td>
<td>0.500</td>
<td>0.465</td>
</tr>
<tr>
<td>Milk (servings/d)</td>
<td>0.402</td>
<td>0.437</td>
<td>0.437</td>
</tr>
<tr>
<td>Cheese (servings/d)</td>
<td>0.165</td>
<td>0.374</td>
<td>0.275</td>
</tr>
<tr>
<td>Yogurt (servings/d)</td>
<td>0.006</td>
<td>0.024</td>
<td>-0.025</td>
</tr>
<tr>
<td>Calcium (mg/d)</td>
<td>0.280</td>
<td>0.328</td>
<td>0.328</td>
</tr>
<tr>
<td>Riboflavin (mg/d)</td>
<td>0.245</td>
<td>0.230</td>
<td>0.273</td>
</tr>
<tr>
<td>Vitamin D (µg/d)</td>
<td>0.135</td>
<td>0.187</td>
<td>0.177</td>
</tr>
</tbody>
</table>

* $p < 0.05$

Ongoing RCT Milk Intervention. Funding: Dairy Research, Inc.

Nutrition at KU ADC

• ~2011
  • Added food frequency questionnaire to KU Alzheimer’s Disease Center (ADC) APEX study

• 2013 Principal Investigator
  • Feasibility of the ketogenic diet in individuals with Alzheimer’s disease.
  • Pilot Funding:
    • KU Alzheimer’s Disease Center
A high-glycemic diet is associated with cerebral amyloid burden in cognitively normal older adults

Matthew K Taylor,1,3 Debra K Sullivan,1,3 Russell H Swerdlow,3 Eric D Vidoni,3 Jill K Morris,3 Jonathan D Mahnken,2,3 and Jeffrey M Burns3

Departments of 1Dietetics and Nutrition and 2Biostatistics, University of Kansas Medical Center, Kansas City, KS; and 3University of Kansas Alzheimer’s Disease Center, Fairway, KS

ABSTRACT
Background: Little is known about the relation between dietary intake and cerebral amyloid accumulation in aging.
Objective: We assessed the association of dietary glycemic measures with cerebral amyloid burden and cognitive performance in cognitively normal older adults.
Design: We performed cross-sectional analyses relating dietary glycemic measures (adherence to a high-glycemic-load diet (HGLDiet) pattern, intakes of sugar and carbohydrates, and glycemic load) with cerebral amyloid burden (measured by florbetapir F-18 positron emission tomography) and cognitive performance in 128 cognitively normal older adults who provided eligibility screening data for the University Molecular imaging techniques with the use of positron emission tomography (PET) with an amyloid-specific ligand allow for the detection of cerebral amyloid in those with AD (2). This technique is increasingly used as a research tool to detect the molecular pathology of AD in cognitively unimpaired individuals, of whom 20–40% have evidence of cerebral amyloid deposits and are thus considered to be at higher risk of developing AD (3). These individuals are the target of interventional trials to prevent or delay the onset of AD, with an increasing interest in lifestyle behaviors, including dietary approaches (4).
Current studies show that impaired glucose metabolism and peripheral hyperglycemia are associated with a higher risk of
High Glycemic Load Diet Pattern associated with Cerebral Amyloid

Visualization of Relationship between Amyloid & HGL Diet Pattern
n = 128

Standardized β values are projected on the MNI152 anatomical template, with warmer colors representing regions of greater association with HGLDiet.
Featured Article

Feasibility and efficacy data from a ketogenic diet intervention in Alzheimer’s disease

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\textsuperscript{c}Department of Biostatistics, University of Kansas Medical Center, Kansas City, KS, USA
\textsuperscript{d}Department of Neurology, University of Kansas Medical Center, Kansas City, KS, USA
\textsuperscript{e}Department of Molecular and Integrative Physiology, University of Kansas Medical Center, Kansas City, KS, USA
\textsuperscript{f}Department of Biochemistry and Molecular Biology, University of Kansas Medical Center, Kansas City, KS, USA
Ketogenic Diet Participants and Study Design

• **Participants:** 15 individuals with AD + Study Partners enrolled
  7 CDR 0.5
  4 CDR 1
  4 CDR 2

  *All 4 CDR 2s dropped and 1 CDR 0.5 dropped due to caregiver burden*

**Design**

- Baseline Testing
- + Diet Education
- Daily Urinary Ketone Tests
- 1-month visit
- 2-month visit
- 3-month Testing
- 4-month Testing
- Ketogenic Diet
- Washout
Ketogenic Diet Cognitive Results

Individual Change in ADAS-Cog Scores from Baseline - 3 Months

Mean Change in ADAS-Cog Scores

*Participant 05 was diet intervention compliant, but not protocol compliant as cholinesterase inhibitor therapy was discontinued.
Ketogenic Diet Status

- 1 R01 AG060733-01A1
- Validation and Mechanistic Interrogation of Metabolism Targeting for AD
- MPI
  - Russell H. Swerdlow
  - Debra K. Sullivan
- RCT (n = 80)
  - MCT-supplemented Ketogenic diet
  - Therapeutic Lifestyles Diet
- 24th Percentile
Feasibility trial of a Mediterranean diet pattern to prevent cognitive decline

- 2016 Pilot Funding: KU ADC
- Establish whether it is feasible for older adults with and without cognitive impairment to adopt and maintain a Mediterranean diet pattern for 6 weeks.
- Evaluate the acceptance and sustainability of the MedDiet pattern
Feasibility trial of a Mediterranean diet pattern to prevent cognitive decline (n=30)

**Demographics and Feasibility**

<table>
<thead>
<tr>
<th></th>
<th>Probable AD N = 12</th>
<th>Cognitively Normal N = 18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>77.4 ± 3.9</td>
<td>71.6 ± 5.2</td>
</tr>
<tr>
<td>Gender (%Male)</td>
<td>75%</td>
<td>29.4%</td>
</tr>
<tr>
<td>Completion Rate</td>
<td>80%</td>
<td>94%</td>
</tr>
<tr>
<td>Food box adherence</td>
<td>100</td>
<td>100</td>
</tr>
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</table>

Reasons for attrition: change in health status and time burden.

**Change in Diet Intake**
Biomarker of Fruit/Vegetable Intake
“Veggie Meter”

Subset: Change in Skin Carotenoid Levels (n=12)

Skin Carotenoid Levels

Baseline
End

p = 0.006
NICE STUDY

Nutrition Interventions for Cognitive Enhancement

“Enhanced Mediterranean Diet for Alzheimer's Disease Prevention”

• 1 R01 AG060157-01

• MPI
  • Debra K. Sullivan
  • Jeffrey M. Burns

• RCT (n = 200)
  • Enhanced Mediterranean diet pattern
  • Low Fat diet pattern

• Awarded 9/30/2018 – 5/31/2023
Training Future Researchers

• Lauren Ptomey, PhD, RD
  • PhD Weight management in IDD
  • R01 Remote exercise in IDD

• Matthew Taylor, PhD, RD, LD
  • PhD ketogenic diet
  • Post doctoral fellow
  • K01 submission February 2019

• Sibelle Alhayek, MS
  • PhD student

• Brooke Noble, MS, RD
  • PhD student

• M.S., R.D. students
  Emily Cope  Olivia Nast  Kristy Taylor
  Randy Evans  Katherine O’Dell  Alyssa Klehr
  Rachel Sandoval  Jordan Chen  Michelle Nussbaum
  Katelynne Burghardt  Kayla Graves  Cassie McClellan
Empowering Community Through Science and Care
Mission

To improve the lives of patients and families with Alzheimer’s disease by eliminating the disease through research into its treatment and prevention.

Core Values

Meaningful Work
Always Improving
Driving Innovation
Empowering Community
Overview

• Recruitment Innovation to Speed Trials and Improve Experience
  • Centralized model
  • Real-time recruitment metrics

• Translating Clinical Research to Lifestyle Modification Support
  • Aerobic exercise (TEAM, ADEPT, APEX), ketogenic (KDRAFT), and Med. diet (NICE)
  • Lifestyle Empowerment for Alzheimer’s Prevention (LEAP! / LEAP!Rx)

• Engagement & Empowerment Through Knowledge
  • AD education developed and delivered with the community
  • Building collaborative care networks throughout KS
Adopted CRO-like model shifting burden off study coordinators

• Major investment in centralized recruitment infrastructure and personnel (Vidoni et al., 2018)
  
  • 4x increases in participation inquiries
  
  • 54% decrease in enrollment time
  
  • Real-time recruitment metrics via R/Shiny
  
  • EMR research referral and e-consent for medical record release
• Translational education program on AD-risk reduction through lifestyle modification

• Empowers successful behavior changes that promote brain health and overall wellness

• Provides evidence-based recommendations on nutrition, physical activity, and more for brain health

• 1300+ individuals have taken the LEAP!
Developing culturally appropriate versions of LEAP!

• African-Americans - *Aging With Grace*
  - 47 times to over 700 individuals

• Latinos - *¡Envejecimiento Digno!* (Perales, *Ethn Health*, 2018)
  - 12 times to 145 individuals

• Rural residents – *Wheat State LEAP! for rural KS* (Blocker, in prep)
  - 71 rural KS residents completed 12 week intervention
  - Increased steps and dementia knowledge

T. Weatherspoon
Jaime Perales
Erin Blocker

KU Alzheimer's Disease Center
The University of Kansas Medical Center
• LEAP! Engagement methodology being tested in RCT (Burns: R01 AG052954)

• KU Health System physicians prescribe LEAP! through EMR

• YMCA delivers LEAP!Rx over 12 weeks

• 52-week follow-up
Empowering a More Dementia Capable and Research Ready Community

• **Forget Me Not Play** (in partnership with USAA/AAAA, GAP Foundation, and the KC Black Health Care Coalition)
  • Hosted two stagings (n=>500, n=311 completed post-performance surveys)
  • 93% agreed they had “a better sense of why African-Americans need to get involved in research”
  • 17 play attendees came to an *Aging With Grace*
  • 2 individuals enrolled in our Clinical Cohort

![Image of a group of people]
Transforming Dementia Capability in the Region

• Leading *Kansas City Collaborative for Dementia Capability* (Ptomey/Vidoni ACL ALGG0009)
  
  • Implementing RDAD-KC program in the region to support persons with dementia or IDD and their caregivers. *(adapted Teri et al., JAMA 2003)*

• Trained over 200 formal caregivers and professionals on dementia and dementia-capable care
  
  • Regional network of NTG Regional Affiliate Trainers (n=23)

• Enrolled 60 dyads in the RDAD-KC program
  
  • Reduced Unmet Needs and NPI-Q
Create a More Dementia Capable and Research Ready Community

• We emphasize:
  • Collaboration with long-standing community organizations
  • Community-informed research and programs
Innovating New Models of Care

• Aligning Primary Care practices with early detection protocols

• Integrating dementia education and support into provider practice workflow

• Connection disease disclosure to a wellness plan that includes research
Community at the Core

• Improving, Innovating, and Empowering so that our work is meaningful to our region.

• Stakeholders benefit from and inform our work.

• Energy and experience that is transforming recruitment and education, making our region more dementia capable and research ready.
Thanks to my great team!

• Hit us up on SM:
  • @KUALZ
  • fb.com/KUADC
Jaime Perales Puchalt, PhD

- Post-doctoral Fellow, KU ADC
- Expertise in epidemiology of aging and dementia
- Key architect and steward of community partnerships in the Latino community

Becoming an independent researcher in Latino AD disparities
Becoming an independent researcher in Latino AD disparities

Jaime Perales Puchalt, PhD, MPH
(NIA Diversity Supplement: P30AG035982)
Index

1. Previous experience
2. Long-term goal
3. Experience at the KU ADC
4. Conclusions and Next Steps
Index

1. Previous experience
2. Long-term goal
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My previous experience: 2006-2008

Psychometrist and data manager, stress-related projects
My previous experience: 2009-2014

Site manager, COURAGE in Europe Project

My previous experience: 2011-2012

Visiting PhD researcher, QoL in dementia research

My previous experience: 2014-2016

Postdoctoral fellow, Latino Kick Buts

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1. Previous experience
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My long-term goal

• To become an independent dementia disparities researcher among Latinos
KU ADC is ideal for my goal

Latinos as Percent of County Population in the State of Kansas
Latino Percent Equal To or More than 7%

Source: U.S. Census Bureau
Map prepared by: Juntos Center KUMC Preventive Medicine and Public Health on June 9, 2018
KU ADC is ideal for my goal

Latinos as Percent of County Population in the State of Kansas

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Latinos as Percent of County Population in the State of Kansas
Latinos equal to or more than 7%

ADC Goals:
1. Educate community on AD
2. Support recruitment
3. Coordinated care
Addressing gaps to reach my goal

NIA Diversity Supplement (P30)

Long term goal: Independent dementia disparities researcher among Latinos

Goal 1. AD clinical research methods

Goal 2. Collaborative networks

Goal 3. Skills to achieve research independence
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4. Conclusions and Next Steps
1. Our Latinos needed AD education

- AD education
- AD assessment & care
- AD prevention
- Financial assistance for AD
- Caregiver support

Served Latinos
Professionals

kualzheimer.org
1. I developed an AD educational tool for Latinos

- Borrow-Sanchez, 2011
1. Envejecimiento Digno increases AD knowledge
1. I harvested Envejecimiento Digno’s success

New amigos! Publication!
1. I have educated >60 Latinos ever since
2. Our Latinos needed AD assessments
2. Our Latinos needed AD assessments

<table>
<thead>
<tr>
<th>Service</th>
<th>Served Latinos</th>
<th>Professionals</th>
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<tbody>
<tr>
<td>AD education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AD assessment &amp; care</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AD prevention</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Financial assistance for AD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caregiver support</td>
<td>10%</td>
<td>20%</td>
</tr>
</tbody>
</table>

Under-detection

Under-representation

Stone

kualzheimer.org
2. I trained in AD assessment

- Cognitive testing
- Clinical dementia rating
- Consensus meetings
2. I led the integration of UDS 3.0-SP
2. I promoted UDS as a chance to assess memory

Senior centers  Religious centers  Latino media
2. I enrolled 30 Latinos in 10 months

Envejecimiento Digno increased research motivation

48 Latinos interested in Cohort

Recruited and assessed 30 Latinos in 10 months

Severe previous underscreening

Detected 3 undiagnosed individuals
Recent Publications

Published
• **Perales**, et al. (2018): Feasibility of an Alzheimer’s disease knowledge intervention in the Latino community; Ethnicity & Health
• Burns, Watts, **Perales**, et al. (2018): The Impact of Creative Arts in Alzheimer’s Disease and Dementia Public Health Education; Journal of Alzheimer’s Disease
• **Perales** et al. (2018): Cardiovascular health and cognitive function among Mexican older adults: cross-sectional results from the WHO Study on Global Ageing and Adult Health; International Psychogeriatrics
• Vidoni, **Perales**. (2017): Aerobic Exercise Sustains Performance of Instrumental Activities of Daily Living in Early-Stage Alzheimer Disease; Journal of Geriatric Physical Therapy

Under review
• **Perales** et al. (Submitted to Ethnicity & Health): Using a theater play as an Alzheimer’s disease outreach strategy
• **Perales** et al. (Submitted to International Journal of Geriatric Psychiatry): Cardiovascular health and dementia incidence among older adults in Latin America: results from the 10/66 Study.
• **Perales** et al. (Submitted to International Journal of Geriatric Psychiatry): Risk of dementia and mild cognitive impairment among older adults in same-sex relationships
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1. Previous experience
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Conclusions

KU ADC + Diversity Supplement = more independent AD disparities researcher
• Latino partnerships
• Clinical dementia assessment
• Leadership

We have been able to address some Latino AD disparities
• Knowledge
• Research participation
• Detection
Next steps

K01 on implementing AD services in primary care among Latinos (NIMHD)

• Training
  • Evidence-based AD care
  • Health systems research
  • Community based participatory research
Moltes gràcies!
¡Muchas gracias!
Thank you very much!

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Fairway, KS 66205
913-588-0555
kualzheimer.org
Michelle Niedens, LSCSW

- Director, MyAlliance for Cognitive Health
- Premier regional resource for Alzheimer’s care.
- 18 years with the Alzheimer’s Assoc. Heart of America Chapter as Director of Education, Policy and Programming
MyAlliance for Cognitive Health: Shifting the Point of Care

Michelle Niedens, L.S.C.S.W.
Statewide Community Care Network: MyAlliance for Cognitive Health

Mission: Improve the health of all Kansans at-risk or living with dementia

What is MyAlliance?
- Tiered approach to dementia management
- Partnership with PCPs
- Protocols for early detection
- Social Work Navigators embedded in clinic for post-diagnosis support

Towards a dementia-ready community
- Streamlines access to optimal care
- Delivers right care to right patients

- Primary Care Physician Partner
  - Diagnostic Tools, clinical care
  - Reach 100%

- MyAlliance Navigator
  - Disease Education, Support and Resources linkages
  - Reach 50%

- Co-Management Clinic
  - Multi disciplinary team lead by dementia specialized nurse practitioner
  - Reach 25%

- ADC Memory Clinic
  - Reach 10%
Key Features of MyAlliance

**Informed by**
- Minnesota Act On Alzheimer’s
- KU Heart and Stroke Collaborative
- Indiana Healthy Brain Aging Center
- Johns Hopkins MIND at Home Project
- Cleveland Managed Care Project
- North Central Texas REACH II Program
- Kansas Bridge Project

**Informed by**
- Self-sustaining
  - CMS Chronic Care Management (CCM) billing
- Research Recruitment Mechanism
  - Change the culture of recruitment in the community
- Education / Workforce development
- Early Recognition
- Shift support to Patient Empowerment Model
Current Dementia Recognition in Primary Care

- MCI/Early Stage
  - Less likely to identify concern
  - Concerns vague
  - Lack of agreement among family members
  - Told diagnosis 45% of the time

- Middle Stages
  - Medicare Wellness Checks
  - Complaint
  - MMSE
  - Care Complications

- Later Stages
  - Have operated as if a diagnosis
  - Went entire distance in disease with general dementia diagnosis
  - ‘Wish I would have known’
Current screening tools utilized:

<table>
<thead>
<tr>
<th>Cognitive Screen used in Annual Medicare Wellness Visit</th>
<th>Providers = 204</th>
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<tbody>
<tr>
<td>MMSE</td>
<td>165 (81%)</td>
</tr>
<tr>
<td>General Question then MMSE</td>
<td>12 (6%)</td>
</tr>
<tr>
<td>MoCa</td>
<td>15 (8%)</td>
</tr>
<tr>
<td>Slums</td>
<td>11 (5%)</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
</tr>
</tbody>
</table>
Early Detection and Diagnosis of Memory Disorders by Primary Care

MCI/Eary Stage
- Medicare Wellness Visits
- AD-8
- MoCa
- Dementia Evaluations

Middle Stages
- Integration of NPI-Q
- Direction of Care Complications
- Informed families

Later Stages
- Stronger voice of the person in end of life decisions
- Reduced ‘accidental’ futile efforts
- Family preparation
Users vs. Non-Users of Community Resources – Lessons in the Literature

**Users**
- Care partners
  - More educated
  - Greater level of burden
- Patients
  - More cognitive and functional impairments
  - More behavioral problems
  - Reduced activities due to cognitive impairment

**Non-Users**
- Care Partners
  - > 70% of all care partners
  - Less depressed
  - More social supports
- Patients
  - Less cognitive and functional implications
  - Fewer behavioral problems
Practice Based Semi Structured Interviews on Use of Care Coordination/Support

- 59% had either embedded social workers or care coordination/health navigation staff.
- Vast majority of Social Workers/Navigators report little to no experience with dementia.
- Utilized for imminent need.
- Focus on limited range of chronic conditions.
Application of a patient empowerment model

• Changing language from “care plans” to “wellness plans”

<table>
<thead>
<tr>
<th>Navigator Roles</th>
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<tbody>
<tr>
<td>Care coordination</td>
</tr>
<tr>
<td>Disease Education</td>
</tr>
<tr>
<td>Post-diagnosis Emotional Support</td>
</tr>
<tr>
<td>Driving and Safety</td>
</tr>
<tr>
<td>Health Promotion</td>
</tr>
<tr>
<td>Access community resources</td>
</tr>
<tr>
<td>Self Advocacy including active role in decision making</td>
</tr>
<tr>
<td>Build support system capacity</td>
</tr>
<tr>
<td>Design compensatory systems</td>
</tr>
<tr>
<td>Access to research opportunities</td>
</tr>
</tbody>
</table>
Integration of Patient Empowerment Model

- **MCI/Early Stage**
  - Patient Empowerment
  - Advocacy
  - Research Involvement
  - Active Planning
  - Post Dx Counseling

- **Middle Stages**
  - Behavioral/Mood complications
  - Caregiver Burden
  - Premature Disability
  - Institutionalization
  - Exploitation/Self Neglect

- **Later Stages**
  - End of Life decisions
  - Family Conflict
  - Compounded grief issues
Research Recruitment Components

• Sustainable research recruitment network
  • Built on a high-value clinical care program (funded via Medicare CCM codes)

• Increase access points to research
  • Patients
  • PCPs
  • Community Stakeholders
    • Black Health Care Coalition
    • El Centro
    • Expand research connections to community support networks

• Potential to change the culture of research participation for PCPs and Patients
Educational Components:

• Expand number of social workers with dementia specific focus.
  • Strengthen curriculum in social work programs in the region through partnership
    • Dementia Intensive (Joint effort of 8 Social Work Schools/Departments)
    • Participation in Integrated Health Scholars Project
  • MentorD
    • Provide year long dementia education and mentorship program for social workers
    • Modified version for adjunct navigators
    • Modified version for community health workers
• MyAlliance PCP partnerships
  • Use of Minnesota Act on Alzheimer’s Provider Webinars
  • MyAlliance Provider Partners Program (Modified from Wash U curriculum)
  • Newsletter and Annual Dinners
Educational Components (continued)

• PAIRS  (Inspired by Northwestern Buddy Program)
  • 6th Year

Scott Koppel, MD, PhD Student
Summary

• Develop a dementia capable community health system
• Increased opportunity to participate in research for patients and PCPs
• Proactive disease management
  • Early recognition, focus on wellness
  • Reduce health care costs
• Opportunity to train front line health care workers in dementia care