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PAD 2020
The Campaign to Prevent Alzheimer's Disease by 2020

Perelman School of Medicine
University of Pennsylvania

Marian S. Ware Alzheimer Program

STATE OF THE SCIENCE CONFERENCE ON THE ADVANCEMENT OF ALZHEIMER'S DIAGNOSIS, TREATMENT AND CARE

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WORKGROUP FINAL REPORTS

June 22, 2012

BIOMARKERS

CLINICAL CARE and HEALTH SERVICES RESEARCH

ECONOMICS, POLICY and ETHICS

DRUG DISCOVERY

“State of the Science Conference on the Advancement of Alzheimer’s Diagnosis, Treatment and Care”

Alzheimer’s Disease Drug Discovery Working Group Recommendations

Working Group Members: Kurt R. Brunden, Franz F. Hefti, Michael Hutton, Virginia M.-Y. Lee, Steven Paul, Ronald Petersen, Dale Schenk and John Q. Trojanowski,

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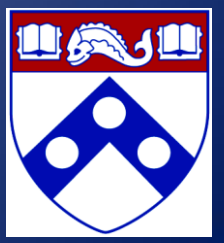

AD Drug Discovery

The top 3 priorities for this workgroup:

- #1: Increase NIH grant support for research on understanding AD disease mechanisms and identifying new AD drug discovery targets by ≥$50M/yr.
- #2: Create a workgroup to make recommendations on revising the regulatory process with the FDA. Workgroup to include thought leaders, advocacy groups and sponsors.
- #3: Regulatory agencies should increase flexibility in considering alternative clinical endpoints (e.g., MCI conversion rate).

AD Drug Discovery

- Identification of new drug targets
- Rally support for increased research funding from NIH for AD
  - Priority #1 for this workgroup is the recommendation to increase NIH grant support directed to understanding AD disease mechanisms and new targets by ≥$50M/yr.

AD Therapy Development

- Explore the use of existing or new biomarkers as earlier readouts of target engagement and drug efficacy
  - Increase efforts to establish FDA-approvable surrogate markers in clinical trials.
  - Increase NIH funding for new imaging methodologies and biomarker identification.
- Improve phase III clinical trial success rates through
  - Improved trial design and endpoints
    - Seek greater patient input during trial design.
  - Enrichment and stratification of subjects
    - Utilize existing biomarkers (CSF, imaging) to improve patient selection for clinical trials. When available, utilize new biomarkers to exclude patients with concurrent co-morbidities (e.g., Lewy bodies, TDP-43).
  - Improved target selection
    - Recognize the continued need for new and improved drugs to treat AD cognitive symptoms.

AD Therapy Development

- Perform trials in early mild cognitive impairment with appropriate design and endpoints
  - Recognition that longer clinical trials may be necessary
  - Priority #3 from this workgroup is that regulatory agencies should increase flexibility in considering alternative clinical endpoints (e.g., MCI conversion rate).
  - Encourage inclusion of cognitive assessment in NIH-funded clinical trials of other age-related diseases (e.g., diabetes, cardiovascular) to provide insight into shared disease mechanisms or AD risk factors.
- Evaluate non-pharmacological interventions including lifestyle modifications
  - Encourage more systematic analysis and rigorous clinical trial design to conclusively demonstrate lifestyle benefits.
- Promote greater data sharing
  - Create a unified database where clinical trial cognitive and biomarker data from placebo groups can be shared from all AD trials. Ideally, also gather and share biospecimens collected from AD trials (5yrs within completion).

Regulatory Aspects

- Shorten the timeline between initial target selection and product approval
  - Priority #2 from this workgroup is to create a workgroup to make recommendations on revising the regulatory process with the FDA. Workgroup to include thought leaders, advocacy groups and sponsors.
  - Consider creating a system for “conditional approval” of AD drugs pending larger pivotal trials.

AD Treatment Recommendations

- Consider increased focus on palliative and cognitive approaches as well as co-morbidities
  - Recognize that drugs targeted to co-morbidities such as PD will be needed for many AD patients.
- Prepare for the consequences of a successful approval of an AD disease-modifying agent
  - Increased demand for biomarker testing
  - Increased demand for genotyping

Collaborative Issues for AD Drug Development

- Encourage existing models of public private partnerships (e.g. ADNI and AARR) to spur drug development
  - Promote industry-academic collaborations directed to new target identification and drug discovery.
  - Industry-academic partnerships will require effective and pragmatic technology transfer groups within universities.
- Explore strategies to incentivize pharmaceutical investment in AD drug discovery and development
  - Extension of product exclusivity
    - Consider patent extensions for AD drugs
    - Consider orphan drug-like exclusivity for first-in-class AD drugs.
  - Government partnership for long-term prevention trials

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BIOMARKER WORKGROUP POST-DISCUSSION RECOMMENDATIONS

Working Group Members: Steven E. Arnold, Kaj Blennow, Giovanni Frisoni, Colin Masters, Gerard Schellenberg, Leslie M. Shaw, Holly Soares, Reisa Sperling, Vivianna Van Deerlin and David Wolk

presented by:

Colin Louis Masters, MD, MBBS, FRC Path

Executive Director, Mental Health Research Institute

Laureate Professor, The University of Melbourne

BIOMARKER WORKGROUP PRIORITY 3 RECOMMENDATIONS

- There was consensus that the principal biomarkers (amyloid-β imaging, volumetric MRI, FDG-PET, CSF amyloid-β and tau) can assist in the differential diagnosis of neurodegenerative disease dementias and may have prognostic value in early symptomatic patients.

- In the absence of a definitive disease-modifying treatment, they may be used clinically on an individualized basis depending on the therapeutic and life planning value to the patient.

- Apply standards used in genetic testing and counseling to ensure confidentiality and to prevent misuse of biomarker data.

BIOMARKER WORKGROUP PRIORITY 2 RECOMMENDATIONS

- Further research is recommended to determine the value of disease diagnosis and prognosis for health, quality of life and economic outcomes. When a disease-modifying intervention is available, biomarker testing (likely including multiple biomarkers) will be necessary.

- Given the recent approval of Amivid and the likely approval of other biomarkers in the near future, we strongly recommend that all data from these clinically ordered tests be required to be placed in a Phase IV database. This is an immediately actionable recommendation that should be promoted by advocacy groups to appropriate government agencies.

BIOMARKER WORKGROUP PRIORITY 2 RECOMMENDATIONS

- Discovery and validation of more sensitive and specific cognitive markers needs to be a major focus of research. Such measures may be most cost effective for screening and as outcome measures with obvious face validity. The relationship between cognitive markers and biomarkers will need to be established.

- Focus new biomarker discovery on a general marker of neurodegeneration, e.g., synaptic integrity as well as other pathological processes, e.g., TDP-43, vascular disease, α-synuclein.

BIOMARKER WORKGROUP PRIORITY *2* RECOMMENDATIONS

- Incorporate education and training for physicians in the communication of biomarker data and counseling in formulating diagnosis and prognosis.

- Recommend that medical boards, licensing bodies, and professional societies establish certification or qualifications for the conduct of biomarker testing, interpretation of data and appropriate quality assurance programs.

BIOMARKER WORKGROUP PRIORITY *1* RECOMMENDATIONS

- Complete standardization of existing principal biomarkers of interest: , amyloid-β imaging, CSF amyloid and tau, MRI topographic volumetry (e.g., hippocampus) and FDG-PET. These should include standard operating protocols for acquisition, assays, data processing and the establishment of normative values. Ongoing harmonization and standardization initiatives for biomarkers should be accelerated for presentation to regulatory agencies.

- Longitudinal studies that include and compare multiple biomarkers using standardized protocols need to be enlarged, extended in time and expanded to include samples that better reflect the general population.

BIOMARKER WORKGROUP PRIORITY *1* RECOMMENDATIONS

- Early and frequent biomarker testing should be incorporated into clinical trial designs to assess how well biomarkers over short durations (e.g., 3 months) allow recognition of longer-term response to therapeutic intervention.

- Focus new biomarker discovery on biomarkers that reflect current disease activity. This may be helpful to more sensitively measure rate of decline and therapeutic response.

CLINICAL CARE AND HEALTH SERVICES RESEARCH (CCHSR)

Workgroup Participants

Sube Banerjee, Matthew Baumgart, Kathleen C. Buckwalter, Meryl Comer, Lynn Feinberg, Renato Maia Guimaraes, Lisa P. Gwyther, Katie Maslow, Diane E. Meier, Mary D. Naylor, Mark A. Sager, Sidney M. Stahl

Core Principles

- Focus on the person and family and their needs over time, across the15-year span of illness
- Shift resources and care to the community, home
  - Improve quality, survival, markedly reduce cost
  - Prioritize continuity of relationships
- Integrate, do not duplicate, existing resources
- Assure gains for all key stakeholders
- One-stop shopping for persons, families, clinicians, researchers, educators, and trainees
- Assume major investment in public and clinician awareness through a sustained and professional communications campaign

Vision: The Human Experience of the Illness

- Community-based Memory Centers as a part of the Liveable Communities Initiative
- Single location and clearinghouse for AAAs, ADRCs, clinical assessment and re-assessment, family support services, care coordination, clinical care services, training site
- Feels like a community center or a senior center to persons and families; co-locates clinical care, coordination, Registry, research
- Engage early at the *"something is wrong"* stage and retain over time through clear articulation and delivery of real benefits to persons and families

BRING THE CARE TO PERSONS AND THEIR FAMILIES

- Integration in one place of healthcare and social services for persons and families; Registry; Research
- Identify best practices, package into transferable skill sets as technical assistance designed to meet the needs of afflicted persons, families, clinicians
- Assure implementation through social marketing, use principles of diffusion of innovation, communications, and audience research
- Training site for the workforce
- Standardized, valid and actionable metrics, ultimately linked to payment
- Registry - person and family (longitudinal data)
- Co-located research infrastructure for clinical trials

RESEARCH PRIORITIES

- Focus on assessing family needs and capacities, test a range of support options
- Health services research on diverse delivery models and fit at different stages of illness, different levels of family need and capability.

Research Priorities, cont'd

- Test effect of community care model(s) on key clinical and utilization metrics, overall and within subgroups (e.g., diverse communities)
  - **National Registry**
    - Standard data elements
    - Longitudinal assessment
  - Assess impact of on population health models such as ACOs
- Assess needs over time
  - Quality of life (person/family), satisfaction with care
  - Survival
  - Person and Family Needs Assessment
  - Resource Utilization
  - Costs

Implementation: The What, Who, When, How

What: The Action Plan

- Explore integration of these priorities into NAPA via Advisory Council, other
- Articulate the value proposition for the key stakeholders
- Cultivate the key stakeholders
  - NIA, NINR, AHRQ, CDC, AoA, HHS/CMS/CMMI, AGS, GSA, etc
  - Alzheimer's Association, AARP, Caregiver orgs
  - Foundations, philanthropic sources
- Examine and implement lessons learned from existing "best practices", eg PACE, palliative care, internat'l models
- Propose and advocate for required regulatory changes/rule making to Secretary of HHS

Pathways to Implementation

Who: The Leadership Plan

- Seek input of major leadership groups in the field and identify and support the best entity or persons to take the lead on this initiative and make the case.
- Leadership is the single most important predictor of success.

When: Now

Implementation

How: Resources Needed

- $250K to establish plan over 6-12 months to conduct:
  - Value proposition analysis by stakeholder group, benefits and costs
  - Budget implications: new dollars versus redeployment of existing dollars
  - Cultivation/engagement of stakeholders
  - Environmental scan of existing best practices, proven models, create technical assistance
  - Coalition building, organizing for advocacy

ECONOMICS, POLICY AND ETHICS

Workgroup Participants

Ron Brookmeyer, Kenneth Covinsky, Colin Green, Jason Karlawish, Claudia H. Kawas, David M. Kent, Ara S. Khachaturian, Lewis H. Kuller, Kenneth M. Langa, Robert W. Mahley, Peter J. Neumann, Mary Sano, Yaakow Stern, David R. Weir

ECONOMICS, POLICY AND ETHICS:

Recommendation #1

- As the value of biomarkers and other risk factors emerge and become clinically useful, patients and society will be better served if they think of these measures not as labels of a category, such as preclinical Alzheimers disease, but instead as one, but not the only, measure of risk for disability as a result of progressive cognitive decline.

ECONOMICS, POLICY AND ETHICS:

Recommendation #2

- All patients who are tested for Alzheimer disease biomarkers, such as CSF and PET amyloid, should be included in a registry. In addition, population-based and longitudinal data … will provide an essential foundation for the development of methods to assess health outcomes, and to assess the value and impact of the widespread use of new diagnostic and therapeutic interventions. As robust data are needed to assess real world situations, an inventory is needed to systematically review existing data sources and to identify critical gaps in data and knowledge.

ECONOMICS, POLICY AND ETHICS:

Recommendation #3

- Sate and federal legislatures, NAPA, the Alzheimers Association, the ABA and other relevant organizations should review and propose appropriate revisions to existing laws, institutions and social structures – such as employers, insurers, housing and schools – to assure that they will protect the rights and interests of persons who have had an Alzheimers biomarker test. Particular attention is needed to legal and insurance and work place settings. Until the clinical value of a biomarker test is fully understood, it should not be considered in insurance coverage decisions.

ECONOMICS, POLICY AND ETHICS:

Recommendation #4

- Clinicians need best practice standards on when to order biomarker tests, what to disclose, and how to disclose and interpret results to patients. NAPA should call for the development and dissemination of these standards.

ECONOMICS, POLICY AND ETHICS:

Recommendation #5

- To make the best use of established and emerging biomarkers and other risk factors for Alzheimer's disease, an important goal of the Alzheimers disease research community should be to develop and validate a risk-stratification model for the development such as MCI or dementia, in order to guide clinical and care management decisions by patients, families, and health care providers; as well as policymaking and research to test new interventions.

ECONOMICS, POLICY AND ETHICS:

Recommendation #5, cont.

- This risk stratification model should be developed using data from representative population-based samples so as to accurately represent the clinical complexity of typical older adults, and the resulting competing health risks (e.g., heart disease, diabetes, cancer) that may have an important impact on life expectancy, and, therefore, the efficacy and value of drug and other interventions to prevent or treat Alzheimer's disease.

ECONOMICS, POLICY AND ETHICS:

Recommendation #5, cont.

- Risk-stratification models should be in the public domain, and should be evaluated and updated by a public body (e.g. HHS) using established standards for the reliable and valid measurement of AD risk factors, including the standardization of AD biomarkers. The ongoing evaluation of risk-stratification models should include assessments of the costs (e.g., unnecessary treatment and treatment side-effects) that result from mis-classification when using the models.

ECONOMICS, POLICY AND ETHICS:

Recommendation #6

- Measures of function such as the instrumental activities of daily living are largely suitable for stages of cognitive impairment seen in persons with dementia. Research should be focused on developing more robust non-cognitive measures (such as in the areas of employment and community/social engagement, and mood) for individuals in younger age cohorts and those in presymptomatic stages of AD.

ECONOMICS, POLICY AND ETHICS:

Recommendation #7

- As the value of biomarkers continues to emerge, efforts should focus on the development of efficient methods to produce and evaluate health outcomes, such as the cost of informal caregiving, that are important to society.

ECONOMICS, POLICY AND ETHICS:

Recommendation #7, cont.

- Methods used to model disease progression for the purposes of CEA should use model structures that (a) capture the natural history of disease, (b) consider geographically different populations, (c) incorporate co-morbid health conditions, and (b) use data sourced from systematic review of available evidence.

ECONOMICS, POLICY AND ETHICS:

Recommendation #7, cont.

- Cost effectiveness analyses for diagnostic and therapeutic interventions for people at risk for Alzheimer's disease should follow good practice guidelines for the conduct of economic evaluations, good practice guidance on modeling in a HTA setting, and follow research recommendations on methodology for assessment of diagnostic technologies.

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