Annotated Bibliography for Genetic Counseling Students
October, 2010
Recommended by Megan Bell

These citations are in addition to selected rotation readings
Most important have *

1. *Galimberti, D. and E. Scarpini, *Genetics and biology of Alzheimer's disease and frontotemporal lobar degeneration.* Int J Clin Exp Med, 2010. **3**(2): p. 129-43.

   This article is a great up to date review of the current knowledge of genetics of Alzheimer's disease and FTD. It provides a brief description of the biology of each disease and includes discusions of genetic associations for familial cases versus sporadic cases. It also discusses the currently known molecular mechanisms for each disease and provides clear explanations of proposed gene mechanisms.

2. Saykin, A.J., et al., *Alzheimer's Disease Neuroimaging Initiative biomarkers as quantitative phenotypes: Genetics core aims, progress, and plans.* Alzheimers Dement, 2010. **6**(3): p. 265-73.

   This article is a short summary of current directions and findings by the Alzheimer Disease Neuroimaging Initiative (ADNI). A brief description is provided for each aspect of the study including GWAS, imaging, biomarker, and copy number variant studies. It includes a brief summary of initial findings of each study area, and includes future directions to pursue. It describes it's unique approach of combining imaging and genetics and provides a brief description of initial findings from MRI GWAS studies. These initial findings have identified *APOE* and *TOMM40* as well as SNP's located in the genes EFNA5, *CAND1*, *MAGI2*, *ARSB*, and *PRUNE2* as having potential risk modifying effects.

3. Linnenbringer, E., et al., *"I know what you told me, but this is what I think:" perceived risk of Alzheimer disease among individuals who accurately recall their genetics-based risk estimate.* Genet Med, 2010. **12**(4): p. 219-27.

   This article analyzed Alzheimer disease risk recall of healthy patients after 6 weeks of learning APOE status and compared the recall to their perception of their risk. Just over half of the participants recalled their actual risk percentage accurately. Among those who had accurate recall, about half did not have perceived personal risks that matched their actual risk. It was found that baseline perceived AD risk, baseline feelings of control over AD, and genotype information were the strongest predictors of these discordant risk perceptions. This study provided genetic counseling prior to genetic tests and required participants to have an in-person result session. Overall, this is a good paper that demonstrates that despite appropriate counseling on risk assessment, percieved personal risk may be discordant due to other factors.

4. Cassidy, M.R., et al., *Comparing test-specific distress of susceptibility versus deterministic genetic testing for Alzheimer's disease.* Alzheimers Dement, 2008. **4**(6): p. 406-13.

   This article loked at impact of results of APOE susceptibility testing compared to presenilin or TAU deterministic testing for participants in the REVEAL study. Participants for the susceptibility tests were primarily adult children of patients with a diagnosis of AD, while deterministic testing was offered to participants who were members of a family with detectable mutations in PS1, PS2 or TAU. After genetic conseling, test results were provided and test specific distress was determined by an impact of event scale. Results indicated that participants who tested positive for the APOE e4 susceptibility allele had similar low impact of event scores as those participants who tested positive for a deterministic gene mutation. Among deterministic testing participants, those who received positive results did not experience significantly higher levels of distress compared to those who tested negative. This article is a comparison of 2 preliminary studies, with limited sample size. Also, the deterministic group had limited numbers so that all gene mutations had to be lumped together. This is an interesting preliminary paper, but in order to better determine impact of test results, whether susceptibility testing or deterministic, more research should be done.

5. Chao, S., et al., *Health behavior changes after genetic risk assessment for Alzheimer disease: The REVEAL Study.* Alzheimer Dis Assoc Disord, 2008. **22**(1): p. 94-7.

   This article describes a randomized control study that looked at impact of APOE susceptibility testing on changes in health behavior. Participants were randomized to 2 arms, one being a risk assessment based on family history and sex along with APOE genotyping, and the second being the risk assessment only. Each group was informed of the current therapies and that no intervention has been shown to prevent the occurance of AD. Impact on health beliefs was assessed one year after receiving test results and were assesed by 3 questions. Results indicate that participants who were APOE e4 were more likely to adopt AD specific health changes compared to those who were APOE e4 negative. Limitations to this study are that health change was determined by self reporting and not directly measured. Results from this study could be useful in modifying risk disclosure tecniques to encourage adherance to preventative measures when they are available.

6. Hurley, A.C., et al., *Genetic susceptibility for Alzheimer's disease: why did adult offspring seek testing?* Am J Alzheimers Dis Other Demen, 2005. **20**(6): p. 374-81.

   This study evaluated the reasons 60 adults sought APOE susceptibility testing from participants in the REVEAL study. Participants met with genetic counselors throughout the REVEAL study and were interviewed to evaluate motivations to pursue susceptibility testing. The most commonly indicated motivation included altruism, "to contribute to AD research". The second most common motivation involved utilizing the knowledge for planning, prevention and a need to know. This study utilized grounded theory for it's

methods and the article provides many quotes from the participants. Overal, this article is useful to consider before discussing susceptibility testing with a patient.

7. *LaRusse, S., et al., *Genetic susceptibility testing versus family history-based risk assessment: Impact on perceived risk of Alzheimer disease.* Genet Med, 2005. **7**(1): p. 48-53.

   This article evaluates the impact on risk perception of family history assessment compared to a risk assessment based on being negative for the APOE e4 allele. Participants were enrolled in the REVEAL study and were randomized to 2 arms, one only receiving risk assessment based on family history and gender, and a second arm provided risk assessment based on family history and APOE status. Participants met with genetic counselors to receive risk assessment and impact on perception was evaluated by a written survey. This study found that being negative for the APOE e4 alleles had a bigger impact on risk perception compared to participants who were given similar risk assessment from family history and gender alone. The article discusses that public perception may affect patient's favorable view of genetic information, even though identical risk information was provided to the two groups. This article may be useful to keep in mind when discussing the pros and cons of AD susceptibility testing with a patient.

8. *Mangialasche, F., et al., *Alzheimer's disease: clinical trials and drug development.* Lancet Neurol, 2010. **9**(7): p. 702-16.

   This article provides a review of current directions for drug development for Alzheimer's disease. The article is organized in an accessible manner and is divided into categories depending upon the action of the treatment. Sections include: Cholinergic drugs, Anti-amyloid therapies, Drugs to target TAU protein, Drugs to target mitochondrial dysfunction, Neurotrophins, and other therapeutic strategies including the use of antioxidants. Each section provides a brief description of the goal of each class of drugs and the proposed mechanism, followed by a description of the current drugs in clinical trials and results, if available. This is a great article to orient the reader to the current therapeutic strategies under investigation, as well as providing a review of the current status of these trials as of 2010.

9. Hampel, H., et al., *Biomarkers for Alzheimer's disease: academic, industry and regulatory perspectives.* Nat Rev Drug Discov, 2010. **9**(7): p. 560-74.

   This article reviews the current research being done to find better biomarkers for Alzheimer's disease. It provides brief descriptions of biomarkers in 3 areas: imaging biomarkers, genetic biomarkers, and CSF biomarkers. It provides several useful tables that summarizes the candidate biomarkers in each area. It approaches the use of biomarkers from an industry and research prospective, and makes the argument that biomarkers should be used to evaluate efficacy of therapies instead of neurocognitive and memory assessment. It also discusses the transition of biomarkers from research tools, to being utilized as a clinical and regulatory tool for diagnostic purposes. This article

provides another view of the utility of biomarkers besides the use in research and is particularly useful for the informative tables included throughout.

10. Gates, N. and M. Valenzuela, *Cognitive exercise and its role in cognitive function in older adults.* Curr Psychiatry Rep, 2010. **12**(1): p. 20-7.

    This article reviews the role of cognitive training (CT) in normal aging, MCI, and dementia. It first provides a definition for CT, compared to the other methods with similar names, and describes the current evidence for use of CT in the three groups. It summarizes the methods, findings, and limitations of past studies utilizing CT. It then reviews the current tools used for CT including the use of new technology such as computer programs and game consoles. It concludes with their clinical recommendations which states that CT may have a beneficial effect, and in the absence of any adverse affects should be discussed with patients. They also conclude that computerized multidomain brain training would be the most beneficial, although access and feasability should be addressed before making this recommendation.

11. von Arnim, C.A., U. Gola, and H.K. Biesalski, *More than the sum of its parts? Nutrition in Alzheimer's disease.* Nutrition, 2010. **26**(7-8): p. 694-700.

    This article reviews the current studies done to evaluate the role of nutrition and supplementation in AD. It discusses malnutrition and AD, the role of antioxidants, B-vitamins, and specialized diets. It includes several useful tables that summarizes many of the studies conducted in each area of nutrition. The author concludes with the assessment that nutrition does play an important role in the prevention of AD, and discusses why positive results have been seen by prospective epidemiological studies compared to the often negative results from randomized controlled trials. Areas for future consideration include the analysis of specific micronutrient deficiencies in patients, and the use of an integrated approach of socially and mentally stimulating activities combined with nutritional approaches may be the most beneficial in preventing or slowing the progression of AD.

12. Vernarelli, J.A., et al., *Effect of Alzheimer disease genetic risk disclosure on dietary supplement use.* Am J Clin Nutr, 2010. **91**(5): p. 1402-7.

    This study evaluates the effect of APOE disclosure for 272 unaffected individuals with a family history of AD on dietary supplement use. Data for this study was collected from REVEAL II, and participant data was divided into two groups, those who were APOE e4 positive for at least one allele and those who were APOE e4 negative. Six weeks after receiving their genetic test results, participants answered an 8 question survey evaluating health behavior changes. This study found that e4 positive participants were 4.75 times more likely to take dietary suplements after adjustment for possible confounders. The most common supplement use was vitamin C, E, and botanicals including ginko biloba, curcumin, and green tea. This study suggests that APOE e4 status may impact nutritional changes despite participants being informed that dietary supplements have not been shown to slow or prevent AD. This article provides an interesting discussion of direct to

consumer testing and that the impact of communication of risk assessments should be studied further.

13. Williamson, J., J. Goldman, and K.S. Marder, *Genetic aspects of Alzheimer disease.* Neurologist, 2009. **15**(2): p. 80-6.

    This article discusses the current knowledge of genetic etiology of AD, and more specifically focuses on genes other than Presenilin 1, Presenilin 2, APP, and APOE. It describes candidate genes found on chromosome 9, 10, and 11. This article is particularly useful for it's discussion of genetic counseling and the use of genetic testing in clinical practice. It describes that 5 main points that genetic counseling should address current understanding of genetic etiology of AD, risk factors, testing options and participation in research, DNA banking and autopsy to confirm diagnosis. It concludes with the statement that family history and age of onset are the two most important factors to consider for pursuing testing. It also suggests that if clinical genetic testing is pursued, appropriate genetic counseling should be provided and that a protocol such as the Huntington disease testing protocol may be a useful model to follow.

14. *Wain, K.E., et al., *Living at risk: the sibling's perspective of early-onset Alzheimer's disease.* J Genet Couns, 2009. **18**(3): p. 239-51.

    This article explores siblings' experience with early onset Alzheimer's disease using questionnaires and semi-structured interviews. Questions asessed knowlede, personal risk perception, level of worry, and effect on life decisions. This study found that 46% of the participants were notified of the diagnosis the same day it was provided, and 62.5% indicated that the diagnosis did not change their closeness with their sibling. 88% indicated that they had feelings of grief and loss upon hearing the diagnosis. This article provides many quotations from participants in each area that was asessed. Overall, this paper suggests that each family member responds differently to the diagnosis of dementia in a loved one, and that they may have unique concerns compared to children or caregivers of the patient. Sibling's concern about their own risk as well as grief and impact on life experiences should be considered during consultations with multiple family members.

15. Schutte, D.L., *Alzheimer disease and genetics: anticipating the questions.* Am J Nurs, 2006. **106**(12): p. 40-7; quiz 47-8.

    This article is written for health care practicioners to orient them to the current knowledge, vocabulary and anticipated questions about Alzheimer disease and genetics. This would be useful as a handout for nurse practicioners or other clinic staff as a quick review of Alzheimer's disease and genetics and appropriate responses to anticipated questions.

16. Roberts, J.S., *Anticipating response to predictive genetic testing for Alzheimer's disease: a survey of first-degree relatives.* Gerontologist, 2000. **40**(1): p. 43-52.

This article, although somewhat outdated at 10 years old, still provides some great information about first degree relatives' motivations to pursue predictive genetic testing. 203 participants were provided with a survey, which posed various hypothetical questions and assessed testing intentions. Health beliefs were assessed by measuring perceived threat, perceived likelihood, and concern for developing AD. Hypothetical test situations involved a $200 genetic blood test and addressed 3 situations: test accuracy, meaning of positive result, and available treatment options. Results suggests that first degree relatives would be enthusiastic about pursuing testing in all situations except for a situation in which a positive test result would mean a 50% risk for developing AD. This study indicates that their may be great interest in predictive testing and if there were treatment options available. However, testing such as APOE allele status is susceptibility testing and generally do not provide high risk asessments like those presented in these hypothetical situations. This article suggests that when discussing genetic testing with at risk individuals, test accuracy, meaning of positive result, and available treatment options should be addressed.

17. *Riegman, P.H., et al., *Biobanking for better healthcare.* Mol Oncol, 2008. **2**(3): p. 213-22.

This article is a review of biobanking primarily in advancing cancer research. It presents an overview of the concept of biobanks, appropriate data to collect and link to samples, guidelines and best practices for setting up a biobank, and sample logistics. It discusses evidence based biobanking in the search for appropriate and measurable biomarkers, and presents current ethical, legal and social concerns in biobanking. It discusses the different consent that needs to be obtained to utilize stored tissue for research, access rules, and costs/ monetary sources for sustained support. This is a great review of how a biobank is set up an managed and addresses concerns that one should be aware of when setting up a biobank.

18. Molnar, M.J. and P. Bencsik, *Establishing a neurological-psychiatric biobank: banking, informatics, ethics.* Cell Immunol, 2006. **244**(2): p. 101-4.

This paper discusses the NEPSYBANK, a hungarian national biobank with participation from neurology and psychology departments. This article reviews information about the NEPSYBANK including goals, participants, access, data management, and the utilization of the information to be gained from analysis of tissue samples. This article provides a brief review of how a biobank is set up and the concerns around research for multifactorial disorders such as the neuropsychological diseases.

19. Marcheco-Teruel, B. and E. Fuentes-Smith, *Attitudes and knowledge about genetic testing before and after finding the disease-causing mutation among individuals at high risk for familial, early-onset Alzheimer's disease.* Genet Test Mol Biomarkers, 2009. **13**(1): p. 121-5.

This study evaluated the impact of knowledge of EOAD mutation in first degree relatives of a large Cuban family with a known mutation in Presenilin 1. 56 at risk individuals

completed a survey that addressed attitudes towards possible presymptomatic testing, and the impact on a hypothetical positive test on reproductive decisions. Ten years later, after the mutation was discovered, another questionnaire was sent out to the participants, with 52 of the original 56 responding. Thirty- six individuals were ready for presymptomatic testing at the second survey, with 18 individuals changing their mind over the 10 year span. Reasons for pursing presymptomatic testing including being prepared for the disease, modify of health behavior, and use of the knowledge in planning life choices including work and reproductive decisions. These reasons also changed over the 10 year span with significant changes in the group regarding reproductive decisions. The authors indicate that the findings could be unique to this Cuban family and may not be generalizable to other familes and other cultures. Their conclusions are that individuals opinions of pursuing presymptomatic testing change with increased knowledge about the disease and when there is more certainty about the test.

20. *Kim, S.Y., et al., *What do people at risk for Alzheimer disease think about surrogate consent for research?* Neurology, 2005. **65**(9): p. 1395-401.

This study evaluated the views of individuals at risk for AD on surrogate consent for research. 229 individuals answered a survey that posed 10 hypothetical research situations for a patient with AD. All individuals felt that all 10 scenarios would be accepted by society and had high support for low risk observational studies and random controlled trials. 56% of respondents felt that a higher risk study such as gene transfer or brain biopsy would be acceptable. The acceptability of surrogate consent research was highest when considered from a societal view, and lower when considering a loved one. Overall, there was strong support for surrogate based research with low risk studies, even when there would be no direct benefit for the participants. For higher risk studies, although the support rate was lower, the majority would still find particpation acceptable. This study suggests that medical decision makers for patients with AD are supportive of participation in research, even for altruistic reasons.

21. Kim, S.Y., et al., *Surrogate consent for dementia research: a national survey of older Americans.* Neurology, 2009. **72**(2): p. 149-55.

This study surveyed a random sample of people age 51 and older who participated in the health and retirement study. 1,515 individuals were randomized to one of four surrogate based research scenarios. These 4 scenarios described a lumbar puncture, a randomized controlled drug trial, a vaccine study, and a gene transfer study. Most respondents were supportive of allowing familes to make surrogate consent decisions, even for the gene transfer scenario. Participants were more likely to agree to family consent for the vaccine trial compared to participating in the trial themselves. Findings indicate that black and hispanic respondents are less likely to support surrogate based research. The survey also addressed how much leeway the respondent would allow their surrogate decsion maker, with a majority of respondents allowing some or complete leeway. The results from this study indicate that older Americans would be supportive of surrogate consent for research, even in invasive studies.

22. Jarvik, L., et al., *Children of persons with Alzheimer disease: what does the future hold?* Alzheimer Dis Assoc Disord, 2008. **22**(1): p. 6-20.

This review article describes the current risk factors for children of parents with Alzheimer's disease. It states that there are very few risk estimates available specifically for children of parents with Alzheimer's disease. This article reviews the current (as of 2007) knowledge of genetic risk factors, and other factors such as diabetes, depression and lifestyle. It discusses early markers such as cognitive function, neuroimaging, and potential biomarkers found in CSF. The authors conclude that more research needs to be done to address the following concerns: devising of strategies to determine non-genetic and genetic risk factors, evaluate protective factors, and exploring the usefulness of preclinical changes in biomarkers. The author describes the importance of children of Alzheimer's disease patients participate in research in order to address these concerns.

23. Hsiung, G.Y. and A.D. Sadovnick, *Genetics and dementia: risk factors, diagnosis, and management.* Alzheimers Dement, 2007. **3**(4): p. 418-27.

This article provides a brief, but useful review for clinicians on the current knowledge of risk factors, and genetic testing of Alzheimer's disease and FTD. It provides a good discussion about current predictive genetic testing. It describes the use of genetic counseling for individuals with an unknown etiology for dementia in their family. This provides a useful introduction to the current knowledge of genetic risk factors and provides recommendations for diagnosis and genetic testing strategy.

24. Hiraki, S., et al., *Perceptions of familial risk in those seeking a genetic risk assessment for Alzheimer's disease.* J Genet Couns, 2009. **18**(2): p. 130-6.

This study utilized data from the REVEAL study to determine if perceived personal risk for Alzheimer's disease corresponded to the strength of family history of the disease. 293 first degree relatives of patients with Alzheimer's disease rated their baseline perceived risks and were asked to describe their family history as well as their perceptions of the cause of AD in the family. Strength of family history was significantly associated with risk perception after adjusting for appropriate confounders. Those with more than one relative with AD had an 8% higher baseline risk perception compared to individuals with only one relative with AD. The participants belief in the impact of genetics as a cause for AD did not affect the baseline risk perception, suggesting that association of family history is independent of the individual's belief of the role of genetics. The authors suggest that findings from this study could impact how clinicians provide risk communication, and could also be useful in optimizing coping strategies.

25. Green, R.C., et al., *Disclosure of APOE genotype for risk of Alzheimer's disease.* N Engl J Med, 2009. **361**(3): p. 245-54.

This study evaluated the impact of APOE genotype on anxiety and depression after receiving APOE allele status information. 162 asymptomatic individuals with a parent with Alzheimer's disease were randomly assigned to two groups. One group received

their APOE genetic test results, while the other group did not receive the results. Symptoms of anxiety and depression were measured using the Beck Anxiety Inventory and the Center for Epidemiological Studies Depression scale at 6 weeks, 6 months and 1 year after disclosure or non disclosure. Results indicate that there was not a difference between the disclosure and non-disclosure goup in anxiety, depression, or test related distress. However, the e4 negative group had a lower level of test related distress compared to the e4 positive group. The authors conclude that the data supports the psychological safety of APOE allele testing in individuals screened appropriately. They did suggest that people who are already anxious or depressed may have an adverse psychoogical impact from learning the test results.

26. Garrick, T., et al., *Brain donation for research: who donates and why?* J Clin Neurosci, 2006. **13**(5): p. 524-8.

This study asessed the motivations for brain donation for research in people involved in an Australian brain donation program. 187 people participated in completing a computer based questionnaire that included closed and open ended questions. The highest rated reasons for brain donations include (in descending order) benefit to medicine, benefit to science, benefit to community, access to honest and accurate information, and family illness. Also, the majority (65%) respondents indicated that it was easier for them to decide to donate their brain than to make that decision for a family member. This study suggests that motivations for brain donation are primarily for altruistic reasons and to increase knowledge of the scientific and medical community. Also, it indicates that there may be difficutly in making this decision for a family member.

27. Elliott, B.A., C.E. Gessert, and C. Peden-McAlpine, *Family decision-making in advanced dementia: narrative and ethics.* Scand J Caring Sci, 2009. **23**(2): p. 251-8.

This study evaluated the reasons behind family decision making of 39 individuals with a severely impaired family member in a nursing home. Eight focus groups were conducted and addressed 7 topics including past decision making for their elder, goals for the elder, end of life values, and how conflicts are resolved. Four main themes emerged as motivtions behind decision making: acquisition of decision making authority, decision making for short term and long term frames, justification of decisions, and advocacy for the elders. Participants indicated that justifying decisions involved balancing everyone's interests involved, elder's request and life story, and surrogate's needs. Overall, this is a good qualitative approach at evaluating decision making motivations and concerns of caregivers. This information would be useful when discussing family conflict over decision making and better understanding of the viewpoints of caregivers when making end of life decisions for a family member.