Midwest Alcoholism Research Center: An overview

Andrew C. Heath
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MIDWEST ALCOHOLISM RESEARCH CENTER: AN OVERVIEW

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Spencer T. Olin Professor in Psychology in Psychiatry
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Washington University School of Medicine
GOAL

- To conduct a collaborative program of community-based research on the etiology of alcohol dependence, and associated psychiatric and substance use disorders, to address three etiologic models and five major research questions.

Etiologic Models for Alcohol Dependence

- **Behavioral undercontrol** – what is the role of impulsive traits, attentional problems, and adolescent conduct problems (or problem behaviors) in the etiology of alcohol dependence?

- **Negative affect regulation** – what is the role of negative affect, depression and anxiety disorders and early onset suicidality in the etiology of alcohol dependence?

- **Pharmacologic vulnerability** – what is the role of innate differences in metabolic, subjective, psychomotor and physiologic responses to alcohol, and to nicotine, in the etiology of alcohol dependence?
Major Research Questions

- **Mediating variables**
  What sociodemographic, personality, psychiatric, or other individual difference variables account for genetic (or environmental) influences on risk of alcohol dependence?

- **Risk Modifiers**
  What modifiers/vulnerability factors, genetic or environmental, interact with known risk factors to exacerbate or diminish risk (e.g., under what environmental conditions is the effect of genetic risk increased or diminished – genotype x environment interaction)?

- **Developmental course/natural history**
  Can we identify stage-specific risk factors (genetic or environmental), e.g., different risk or protective factors for initiation of adolescent drinking versus transition to problem drinking versus remission of alcohol problems?

- **Outcomes**
  What are the consequences of adolescent problems with alcohol?

- **Gene discovery**
  Can we use genetic linkage or association approaches to identify novel genetic risk factors for alcohol dependence or associated substance use disorders (e.g., tobacco dependence)?
Approach

- Bring together expertise in diverse areas of alcohol research, represented principally at the three major research universities of the state of Missouri:
  - Washington University School of Medicine – expertise in biological psychiatry, genetic and epidemiologic aspects of alcoholism
  - Saint Louis University School of Public Health – expertise in public health, epidemiologic aspects of alcoholism research
  - University of Missouri–Columbia – expertise in psychosocial, psychobiological approaches to understanding alcoholism etiology and consequences

- Two other institutions collaborate in our research program:
  - Queensland Institute of Medical Research, Brisbane, Australia – provides access to a large number of families with adult twins (>10,000 families), permitting cross-cultural comparisons with a heavy drinking society
  - Palo Alto Veterans Administration, Palo Alto, California – provides additional expertise concerning psychosocial and family study approaches in alcoholism research
The Center’s alcoholism research program is much broader than the scientific cores and three research projects directly funded through the NIAAA Center grant.

Table 1 (later panel) summarizes (most of) the Center’s relevant research and training portfolio that is supported through other research mechanisms. Eight research areas/approaches are represented:
A. Genetic Methodology/Biometrics Projects
Methodological projects involving original theoretical work, computer simulation, and secondary data analysis, that are designed to develop improved methods of collecting and analyzing data on genetic influences on risk of alcoholism and related phenotypes, and their interactions with environmental risk factors.

B. Gene-Mapping Projects
The emphasis here is on projects using community-based rather than clinic-based sampling schemes, and using a Quantitative Trait Locus approach. One funded project is focused on smoking and nicotine dependence (4), but is included here because it is also assessing alcohol-related phenotypes, to take advantage of the overlap of genetic risk factors for alcohol and nicotine dependence. Two (13,15) are using both diagnostic and quantitative indices of alcohol dependence and consumption patterns. A fourth project is using a mutation screening approach to identify genes that contribute to risk of co-occurring alcohol and nicotine dependence. An additional project is pending resubmission (26th percentile).

C. Adult Twin Genetic Epidemiology Projects
Because of the relative maturity of the field of genetic epidemiologic research on alcoholism, these are primarily focused on comorbid phenotypes such as gambling (17,20) where mediators and modifiers of genetic influence are less well understood. Two additional projects, on personality disorder (19) and childhood physical/sexual abuse (18), are pending review.
D. Prospective Studies of Children/Adolescents and Their Families
There are 8 projects focused on children, adolescents or young adults and their parents. These include (i) an African-American family study (21), focused on adolescent siblings and their parents, with oversampling of high-risk families where there is a paternal history of alcohol dependence and/or recurrent drunk-driving convictions; (ii) a twin-family study of childhood Attention Deficit Hyperactivity Disorder (ADHD) (26), a disorder of particular interest because it is observed much more commonly in the children with an alcoholic biologic parent; (iii) a prospective adolescent male twin study of adolescent smoking and nicotine dependence (25) which is coordinated with the MARC adolescent twin project; (iv) a mentored clinician scientist award focused on social phobia and alcohol dependence risk (26), and a second mentored clinician scientist award focused on parental alcoholism and adolescent suicidality (23); (v) a longitudinal study of drinking and high-risk sexual behavior which is following a panel of subjects first assessed as young adults (22). (vi) Finally, the sixth project, as noted previously, is an adolescent twin project focused on adolescent and young adult alcohol problems and dependence, with follow-up assessments at ages 17-25 of participants first assessed at ages 13-19 (24).
E. Children of Alcoholic Twins Projects
Two projects (30,32) are focused on outcomes in the adolescent and young adult offspring of female alcoholic and control twins and their MZ and DZ cotwins. A third project is examining outcomes in the children of parents with both antisocial and alcohol dependence symptoms (31). A fourth project will collect data on the children of a comparison group of drug-dependent twins and their cotwins is pending resubmission (29). These projects will be especially powerful for detecting the environmental influences of parental alcoholism, including those whose effects may depend upon offspring genotype (genotype x environment interaction).

F. College Drinking and After
A 20-year project (33) has completed repeat assessments of student drinking and alcohol dependence, and comorbid problems, through the college years, with follow-up in adulthood. A new cohort is now being recruited, with assessment prior to entry to college, and planned follow-up through the same age range.
G. Pharmacogenetic/Alcohol or Nicotine Challenge/Biomarker Projects
Four projects are using electrophysiological approaches, either in the absence of drug challenge – to identify potential baseline biomarkers of genetic risk of nicotine addiction (35,36), or using nicotine challenge (37,40) to define heritable dimensions of response to nicotine and/or alcohol, which may be associated with differences in alcohol dependence risk.

H. Follow-up Surveys of Adult Community Samples
Two long-term follow-up surveys of adult samples; one of Vietnam veterans, first assessed in 1972-74 (43,44) (with an oversample of veterans identified by urine sample as drug positive upon return from Vietnam; the other of participants in the St. Louis ECA study, first assessed in 1981, to determine the impact of a history of alcoholism on use and costs of health services) (44).
<table>
<thead>
<tr>
<th>PI</th>
<th>Grants Funding Agency</th>
<th>Mechanism</th>
<th>Title</th>
<th>Project Period</th>
<th>Annual Direct Costs</th>
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<tbody>
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<td>A. Genetic Methodology/Biometrics Projects/Date Analysis Projects</td>
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<td>1. R. Heber</td>
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<td>Prospective Examination of Alcohol-Tobacco Comorbidity</td>
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<td>5. R. Price</td>
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<td>Data-Mining Approaches to Suicide and Suicidal Behavior</td>
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<td>Smoking Cessation: The Role of Withdrawal and Dependence</td>
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<td>Symptom Based Transition in Addiction in Male Twins</td>
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<td>Computational Approaches to Substance Abuse Transitions</td>
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<td>Substance Use and Abuse in AAPIs: A Model Minority?</td>
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<td>High-risk Health Behaviors, Health Services Use and Aging</td>
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<td>12. N. Sacco</td>
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<td>B. Gene Mapping Projects</td>
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<td>13. A. Heath</td>
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<td>Molecular Epidemiology of Alcohol Dependence III. EDAC Sib Pairs</td>
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<td>17. S. Eisen</td>
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<td>Pathological Gambling: Causes, Courses and Consequences</td>
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<td>Childhood Trauma, Parental Alcoholism and Comorbidity</td>
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<td>21. K. Bucholz</td>
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<td>Alcoholism: Epidemiologic High Risk Family Study</td>
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<td>22. L. Cooper</td>
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<td>Alcohol Use and Sexual Risk Taking among Adolescents</td>
<td>599-4-04</td>
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<td>23. A. Glownski</td>
<td>NARSAD</td>
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<td>Mothers of Depressed Adolescent Female Twins</td>
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<td>24. A. Heath</td>
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<td>Alcoholism: Genetic Epidemiologic Twin Study</td>
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<td>Genetics of Adolescent Smoking and Nicotine Dependence</td>
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<td>Genetic Epidemiology of ADHD</td>
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<td>28. A. Glownski</td>
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<td>E. Children of Alcoholic Twins/Pseudo-Adoption Projects</td>
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<td>29. K. Bucholz</td>
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<td>Gene-Environment in Outcomes of PSUD Twins' Offspring</td>
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<td>Adult Offspring of Alcoholism Discordant Twins</td>
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<td>31. W. Slutske</td>
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<td>Familial Transmission of Antisocietal Alcoholism</td>
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<td>32. W. True</td>
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<td>Adolescent COAs: A Twin Family Design</td>
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*First year annual direct costs.

*H: University of Helsinki, Finland. K: Karolinska Institutet, Sweden. M: University of Missouri-Columbia. P: Palo Alto VA, California. Q: Queensland Institute of Medical Research, Brisbane, Australia. S: Saint Louis University, W: Washington University. For each grant, the lead institution is listed first. Other institutions may be involved via subcontract, consulting, or co-mentoring relationships.

*NCE: No-cost extension.
Table 1. Research projects and training programs (including grants pending funding or pending review) of MARC investigators.

<table>
<thead>
<tr>
<th>PI</th>
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<th>Project Period</th>
<th>Annual Direct Costs</th>
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<td>A Prospective Study of Offspring of Alcoholics</td>
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<td>34.</td>
<td>T. Trull</td>
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<td>Development of Borderline Personality Disorder Features</td>
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<td>Biobehavioral Markers of Risk for Nicotine Addiction</td>
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<td>36.</td>
<td>A. Anokhin</td>
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<td>Electrophysiological Markers of Vulnerability to Tobacco Dependence</td>
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<td>38.</td>
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<td>Noncontact Sensing of Emotion and Stress Using Laser Doppler Vismetry</td>
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<td>Alcoholics’ Long-Term Use and Costs of Health Services</td>
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<td>R. Price</td>
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**Overall Total Research Project Support (Excluding MARC)**
| Total Training, Other Support MARC | **$9,443,569** |
| MARC-Wide Total Direct Costs (Annual) | **$11,177,323** |

*First year annual direct costs.
*H: University of Helsinki, Finland; K: Karolinska Institutet, Sweden; M: University of Missouri-Columbia; P: Palo Alto VA, California; Q: Queensland Institute of Medical Research, Brisbane, Australia; S: Saint Louis University; W: Washington University. For each grant, the lead institution is listed first. Other institutions may be involved via subcontract, consulting, or co-mentoring relationships.
*NCE: No-cost extension.
MARC Organization: 1. Scientific Cores

♦ **Administrative Core** (PI Heath)
  - Responsible for coordinating the MARC research program, facilitating communications among the five participating sites, monitoring project productivity and human subjects protections, and arranging oversight by the External Scientific Advisory Board and Community Advisory Committee.

♦ **Ascertainment, Tracing and Tracking Core** (PI Madden)
  - Maintains resources for statewide ascertainment of families with adolescent and young adult children, including specialized family types (e.g., minority families, families with twins), and families with children born in Missouri who have since relocated to other parts of the U.S. Monitors productivity, tracking, completion of interview, questionnaire and other assessments of participating family members.
MARC Organization: 1. Scientific Cores (cont.)

♦ **Assessment Core** (PI Todd)
  - Coordinates adult and child assessments (including genotyping), provides interviewer training and maintains quality control for MARC projects, including reliability studies.

♦ **Data Management and Methodology Core** (PI Neuman)
  - Maintains locally-generated databases as well as national databases used by MARC and other investigators. Provides expertise in the latest methods in genetic statistics and other areas of quantitative methodology.

♦ **Pilot Project Core**
  - Provides pilot project support for junior investigators and others who are trying to develop new directions in alcoholism research.
1. **Male Adolescent Twin Study** (PI Heath)
   This is a prospective study of adolescent male like-sex twin pairs, assessed initially at ages 13, 15, 17, 19 and 21, and to be reassessed annually. Parents are also interviewed when a family is first recruited into the study. It is coordinated with two other RO1 projects – a parallel study of female adolescent like-sex twin pairs (PI Heath), now being assessed at ages 19-25; and a study of smoking and nicotine dependence in adolescent male twin pairs, assessed at ages 11-17 (PI Madden).

   - Powerful for testing hypotheses about mediators of genetic influences on adolescent alcohol problems;
   - Powerful for the identification of modifiers of such genetic influences (genotype x environment interaction effects);
   - Powerful for disentangling potentially reciprocal relationships between alcohol dependence and comorbid disorders (e.g., tobacco dependence, depression, suicidality).
2. **Nicotine and Alcohol Challenge Project** (PI Rohrbaugh)
Using young adult smokers and non-smokers (including smoking-discordant twin pairs), this project is investigating the hypothesis that smokers have higher rates of alcohol problems because interactions between nicotine and alcohol (cross-tolerance effects) are leading to reduced levels of intoxication after a standard dose of alcohol in smokers compared to non-smokers. It is further hypothesized, following the work of Schuckit, that lower levels of intoxication after a given dose of alcohol in turn predict increased risk of progressing to heavy drinking, and ultimately to alcohol dependence.

Cross-tolerance effects between nicotine and alcohol have been documented in rodents, but have received little experimental investigation in humans. Three experiments are being conducted, outlined in detail on Poster 29.
3. **Offspring-of-Twins Project** (PIs True and Jacob)

This project is studying the offspring of Australian women who are mothers and twins. It is comparing rates of alcohol problems and other behavioral and emotional outcomes in four groups of offspring:

i. Mother is alcoholic (history of alcohol abuse or dependence) – children are at high genetic risk and high environmental risk;

ii. Mother is not alcoholic, but mother’s MZ twin sister is alcoholic – children are at high genetic risk but low environmental risk;

iii. Mother is not alcoholic, but mother’s DZ twin sister is alcoholic – children are at intermediate genetic risk but low environmental risk;

iv. Mother is not alcoholic, and mother’s DZ twin sister is also not alcoholic – children are at low genetic as well as low environmental risk.

Of course, in these comparisons, it is also necessary to control for comorbid psychopathology in the mothers, as well as alcohol abuse/dependence and other psychopathology in the children’s fathers.

This is a prospective study, with initial assessments of children at ages 13-23. It is coordinated with two RO1 projects focused on U.S. national samples of alcoholic and control Vietnam-era veteran male twins and their cotwins, spouses, and offspring.
A multi-disciplinary team of faculty investigators is taking part in this research program, many with primary appointments in the Department of Psychiatry at Washington University, which has a long history of trans-disciplinary research on alcohol, tobacco, and other drug dependence; but with other investigators drawn from departments as diverse as Otolaryngology, Internal Medicine at Washington University, the Department of Psychological Sciences at University of Missouri–Columbia, and the Department of Community Health at St. Louis University School of Public Health. Five post-doctoral fellows also participate in this research program (Qiang Fu, MD, PhD – Health Psychology; Valerie Knopik, PhD – Psychology and Behavioral Genetics; Christina Lessov, PhD – Behavioral Neuroscience; Amelia Gallitano-Mendel, PhD, MD – Psychiatry; Michele Pergadia, PhD – Health Psychology). Seven faculty investigators are also former graduates from our training program.

Because foreign populations may offer particular advantages for genetic research, foreign collaborators from Australia and Finland are included in our team of investigators, with other collaborations with investigators in Japan, China and the Netherlands under active development.
# Table 2. Faculty Investigators

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Department/Division</th>
<th>Expertise</th>
<th>Research Projects/Science Cores</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Anokhin, PhD</td>
<td>Psychiatry</td>
<td>Psychology, genetics, psychophysiology</td>
<td>35, 36</td>
</tr>
<tr>
<td>K. Bucholz, PhD</td>
<td>Psychiatry, SLU School of Public Health</td>
<td>Epidemiology, genetic epidemiology, adult assessment</td>
<td>8, 21, 29</td>
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<tr>
<td>L. Cooper, PhD</td>
<td>Psychological Sciences, University of Missouri-Columbia</td>
<td>Social psychology, adolescent risky sexual behavior</td>
<td>22</td>
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<tr>
<td>S. Eisen, MD</td>
<td>Internal Medicine</td>
<td>Psychiatric genetics</td>
<td>17, 30, 32</td>
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<td>A. Goate, D Phil</td>
<td>Psychiatry, Genetics</td>
<td>Molecular genetics</td>
<td>13, 14</td>
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<tr>
<td>J. Goebel, MD</td>
<td>Otolaryngology</td>
<td>Dynamic posturography</td>
<td>-</td>
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<tr>
<td>A. Heath, D Phil</td>
<td>Psychiatry, Psychology, Genetics</td>
<td>Behavioral genetics, genetic epidemiology</td>
<td>2, 3, 24, 30, 32, 37, 46</td>
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<tr>
<td>K. Jackson</td>
<td>Psychological Sciences, University of Missouri-Columbia</td>
<td>Genetic epidemiology</td>
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<td>J. Kaprio, MD</td>
<td>Dept. of Public Health, University of Helsinki</td>
<td>Biostatistics</td>
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<tr>
<td>D. Luke, PhD</td>
<td>Community Health, SLU</td>
<td>Psychology, genetic epidemiology</td>
<td>2, 14</td>
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<td>P. Madden, PhD</td>
<td>Psychiatry</td>
<td>Genetics</td>
<td>13, 14, 15, 18, 19</td>
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<tr>
<td>N. Martin, PhD</td>
<td>Population Health, QIMR, Brisbane, Australia</td>
<td>Genetics</td>
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<tr>
<td>E. Nelson, MD</td>
<td>Psychiatry</td>
<td>Psychiatric genetics</td>
<td>8, 26</td>
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<td>R. Neuman, PhD</td>
<td>Psychiatry</td>
<td>Mathematics, statistical genetics</td>
<td>4, 16, 27</td>
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<td>R. Price, PhD</td>
<td>Psychiatry</td>
<td>Sociology, psychiatric epidemiology</td>
<td>5, 9, 10</td>
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<td>W. Reich, PhD</td>
<td>Child Psychiatry</td>
<td>Anthropology, child assessment</td>
<td>24, 30, 32</td>
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<tr>
<td>J. Rice, PhD</td>
<td>Psychiatry, Biostatistics</td>
<td>Mathematics, statistical genetics</td>
<td>13, 14</td>
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<tr>
<td>J. Rohrbaugh, PhD</td>
<td>Psychiatry, Psychology</td>
<td>Psychology, psychophysiology, alcohol and nicotine challenge</td>
<td>38, 39</td>
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<td>N. Saccone, PhD</td>
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<td>Mathematics, statistical genetics</td>
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<td>K. Sher, PhD</td>
<td>Psychological Sciences, University of Missouri-Columbia</td>
<td>High-risk longitudinal research on alcoholism</td>
<td>19, 26, 31, 33, 34</td>
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<tr>
<td>E. Sirevaag, PhD</td>
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<td>Psychology, psychophysiology, alcohol and nicotine challenge studies</td>
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<td>E. Spitznagel, PhD</td>
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<td>Biostatistics</td>
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<td>R. Todd, PhD, MD</td>
<td>Child Psychiatry, Genetics</td>
<td>Molecular neurobiology, psychiatric genetics</td>
<td>16, 27</td>
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<td>T. Trull, PhD</td>
<td>Psychological Sciences, University of Missouri-Columbia</td>
<td>Clinical psychology, personality disorder</td>
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<td>A. Todorov, PhD</td>
<td>Psychiatry</td>
<td>Biostatistics, statistical genetics</td>
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<td>W. True, PhD</td>
<td>Community Health, SLU</td>
<td>Anthropology, genetic epidemiology</td>
<td>29, 30, 32</td>
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<td>H. Xian, PhD</td>
<td>Internal Medicine</td>
<td>Mathematics, statistical genetics</td>
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<td>P. Wood, PhD</td>
<td>Psychological Sciences, University of Missouri-Columbia</td>
<td>Quantitative psychology</td>
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<td>J. Whitfield</td>
<td>Clinical Biochemistry, RPAH Sydney, Australia</td>
<td>Clinical biochemistry</td>
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