Washington State Health Care Authority

Pharmacogenomic testing for selected conditions

Clinical Expert

Jon Montgomery McClellan

Professor, Department of Psychiatry and Behavioral Sciences,
University of Washington, Seattle, Washington

Medical Director, Child Study and Treatment Center (CSTC)

Applicant Name Jon (Jack) McClellan

Address 13925 Par Pl NE
Seattle, WA 98125

1. Business Activities

(a) If you or a member of your household was ***an officer or director of a business*** during the immediately preceding calendar year and the current year to date, provide the following:

Title	Business Name & Address	Business Type

(b) If you or a member of your household ***did business under an assumed business name*** during the immediately preceding calendar year or the current year to date, provide the following information:

Business Name	Business Address	Business Type

2. Honorarium

If you ***received an honorarium of more than $100*** during the immediately preceding calendar year and the current year to date, list all such honoraria:

Received From	Organization Address	Service Performed
AACAP	Washington DC	Institute on Evidence Based Measurement

3. Sources of Income

(a) Identify ***income source(s) that contributed 10% or more of the combined total gross household income*** received by you or a member of your household during the immediately preceding calendar year and the current year to date.

Source Name & Address	Received By	Source Type
University of Washington	Jon McClellan	Salary
Mercer Island School District	Elaine McClellan	Salary

(b) Does any income source listed above relate to, or could it reasonably be expected to relate to, business that has, or may, come before the Committee?

☐ Yes ☒ No

If "yes", describe: Click here to enter text.

(c) Does an income source listed above have a legislative or administrative interest in the business of the Committee?

☒ Yes ☐ No

If "yes", describe: My salary is supported for NIH research grants, and by State funds for my role as medical director of CSTC

4. Business Shared With a Lobbyist

If you or a member of your household ***shared a partnership, joint venture, or similar substantial economic relationship with a paid lobbyist***, were employed by, or employed, a paid lobbyist during please list the following:

(Owning stock in a publicly traded company in which the lobbyist also owns stock is not a relationship which requires disclosure.)

Lobbyist Name	Business Name	Type Business Shared

Provide the information requested in items 5, 6, and 7 below only if:
(a) Your response involves an individual or business if you or a member of your household did business with, or reasonably could be expected to relate to business that has or may come before the Health Technology Clinical Committee.
(b) The information requested involves an individual or business with a legislative or administrative interest in the Committee.

5. Income of More Than $1,000

List each source (***not amounts***) of income over $1,000, other than a source listed under question 3 above, which you or a member of your household received during the immediately preceding calendar year and the current year to date:

Income Source	Address	Description of Income Source

6. Business Investments of More Than $1,000

(Do not list the amount of the investment or include individual items held in a mutual fund or blind trust, a time or demand deposit in a financial institution, shares in a credit union, or the cash surrender value of life insurance.)

If you or a member of your household had a personal, beneficial interest or investment in a business during the immediate preceding calendar year of more than $1,000, list the following:

Business Name	Business Address	Description of Business

7. Service Fee of More Than $1,000

(Do not list fees if you are prohibited from doing so by law or professional ethics.)

List each ***person for whom you performed a service for a fee of more than $1,000*** in the immediate preceding calendar year or the current year to date.

Name	Description of Service

I certify that I have read and understand this Conflict of Interest Form and the information I have provided is true and correct as of this date.

Print Name Jon McClellan MD Click here to enter text.

Check One: ☐ Committee Member ☐ Subgroup Member ☐ Contractor Consulting expert

[redacted]

Signature

1/11/2017

Date

C U R R I C U L U M V I T A E

1. PERSONAL DATA

NAME: Jon Montgomery McClellan, MD

ADDRESSES: Department of Psychiatry
University of Washington
c/o Child Study & Treatment Center
8805 Steilacoom Blvd. S.W.
Tacoma, WA 98498-4771
E-Mail: drjack@u.washington.edu

2. EDUCATION

9/77 - 5/80 University of Michigan (Undergraduate)
Ann Arbor, MI
Honors Chemistry, accepted into Medical School after 3 years (96 credit hours)

9/80 - 6/84 University of Michigan Medical School
Ann Arbor, MI

3. POSTGRADUATE TRAINING

7/84 - 7/87 General Psychiatry Residency
University of Washington, Department of Psychiatry and Behavioral Sciences,
Seattle, WA

7/87 - 6/89 Child Psychiatry Fellowship, and Chief Child Psychiatry Fellow at the University of Washington, Department of Psychiatry,
Children's Hospital, Seattle, WA

4. FACULTY POSITIONS HELD

1989 - 1993 Acting Instructor, Department of Psychiatry and Behavioral Sciences, University of Washington, Seattle, Washington

1993 - 1999 Assistant Professor, Department of Psychiatry and Behavioral Sciences, University of Washington, Seattle, Washington

1999 –2008 Associate Professor, Department of Psychiatry and Behavioral Sciences, University of Washington, Seattle, Washington

2008- Professor, Department of Psychiatry and Behavioral Sciences, University of Washington, Seattle, Washington

5. HOSPITAL POSITIONS HELD

1989 - present	Medical Director of Child Study and Treatment Center, the children's psychiatric hospital for the state of Washington.
1994 - 1995	Acting Co-head, Division of Child Psychiatry, Department of Psychiatry and Behavioral Sciences, University of Washington, Seattle, Washington (temporary assignment).
1994 - 2005	Medical Director, Division of Child Psychiatry, Department of Psychiatry and Behavioral Sciences, University of Washington, Seattle, Washington.

6. HONORS

ACADEMIC HONORS:

1977-80	Honor's College, The University of Michigan
1978-80	Angell Scholar, The University of Michigan
1983-84	Alpha Omega Alpha Honor's Society

PROFESSIONAL HONORS:

1988	Presidential Scholar Award, given by the American Academy of Child and Adolescent Psychiatry.
1993	Child Study and Treatment Center was nominated for the American Psychiatric Association's Gold Achievement Award for outstanding and innovative community program.
1999	"Governing for Results" Recognition by Governor Gary Locke, State of Washington, for Child Study and Treatment Center's Juvenile Forensic Evaluation Team.
2003	Fellow, American Academy of Child and Adolescent Psychiatry
2004	*Dr. Alexander Gralnick Award* honoring excellence for research, treatment and advocacy for children and adolescents with schizophrenia. Child Welfare League of America
2008	Research article "Rare structural variants disrupt multiple genes in neurodevelopmental pathways in schizophrenia" Walsh et al., Science, 2008; was selected as one of the top 100 scientific findings of the year by Discover Magazine.
2008	Research article "Rare structural variants disrupt multiple genes in neurodevelopmental pathways in schizophrenia" Walsh et al., Science, 2008; was highlight as one of the most important papers of the year by Nature.
2008	NARSAD selected the article "Rare structural variants disrupt multiple genes in neurodevelopmental pathways in schizophrenia"

Walsh et al., Science, 2008; as one of the top 10 breakthroughs in schizophrenia research for the year 2008.

7. BOARD CERTIFICATION

BOARD CERTIFICATION:

1991 Board Certified in General Psychiatry
1991 Board Certified in Child and Adolescent Psychiatry

8. CURRENT LICENSE(S) TO PRACTICE

MEDICAL LICENSURE: State of Washington l985, 0023282

9. PROFESSIONAL ORGANIZATIONS

American Academy of Child and Adolescent Psychiatry
International Society for Researchers in Child and Adolescent Psychopathology
American Psychopathological Association

10. TEACHING RESPONSIBILITIES

1) Attending Child Psychiatrist and supervisor for Child Psychiatry Residents, General Psychiatry Residents, Post-Doctoral Psychologist and Psychology Interns (University of Washington) rotation at Child Study and Treatment Center.

2) Excellence in Teaching Award: presented by UW Child Psychiatry Residents, 2006

3) Didactic Presentations:
   a) Child Psychiatry Residents
      i) Antipsychotic Medications
      ii) Psychotic Disorders
      iii) Genetics
      iv) Academic Discussion Group: Seminar Coordinator
      v) Mock Boards, Site Coordinator

   b) General Psychiatry Residents
      i) Early Onset Psychotic Disorders
      ii) Brain, Environment, and Socio-Emotional Development
      iii) Genetics of Schizophrenia

   c) University of Washington Medical Students
      i) HuBio 563: Introduction to Clinical Psychiatry; Psychopathology in Children and Adolescents

ii) HuBio 564: Introduction to Pharmacology II; Psychopharmacology in Children and Adolescents

4) Mentorship
   a) Research Supervisor
      i) Randy Ross, MD (Psychiatry Resident) 1993 – 1995
      ii) Vanessa Walters (UW medical student project) 1998
      iii) Tom Matz (UW medical student project) 1998
      iv) John Pastor MD (3d Year Psychiatry Resident) 2001
      v) Ray Hsiao, MD (3d Year Psychiatry Resident) 2003 – 2006
      vi) Jennifer Cheng Shannon MD (1st Year Psychiatry Resident) 2003 - 2006
      vii) Jeffrey Kaiser, MD (Child Psychiatry Fellow) 2005 – 2007
      viii) Ian Kodish, MD (Psychiatry Resident) 2006 – 2008
      ix) Caitlin Rippey, UW Medical Student (MD/Ph.D. Candidate), 2007 – 2015

5) Awards to Mentored Trainees
   a) Vanessa Walter, University of Washington Medical Student, AACAP Jeanne Spurlock Minority Student Clinical Fellowship in Child and Adolescent Psychiatry, 1998
   b) NIH K23 Grant Award - Mentored Patient-Oriented Research Career Development Award, PI: Wendy Weber, "Controlled Trial of Hypericum for Juvenile Depression." (5K23AT000929). Funding period: 4/1/02 to 3/31/07
   c) NIH K23 Grant Award – Psychotherapy in Adolescent Bipolar Disorder, PI: Stefanie Hlastala, Ph.D, Funding period: 12/2004 – 12/2009
   d) Jennifer Cheng Shannon, MD. APA Training Award for Research. 2005.
   e) Jeffrey Kaiser MD: Career Development Award for Bipolar Disorder, Boca Raton, Florida. 2007
   f) Tom Walsh, Ph.D., Research Assistant Professor, Division of Medical Genetics, University of Washington, NARSAD Young Investigator Award, "Characterization of a brain specific mRNA disrupted by inherited translocation in a young schizophrenia patient." 6/07 – 6/09.
   g) Diane Dickel, predoctoral student, Department of Genetics: "A Genomic Approach to Studying Repeat Instability in Schizophrenia" (NIH Fellowship 1 F31 MH081509). 7/07 – 6/12
   h) Cait Rippey, MSTP student, Department of Medicine: "Rare structural genomic variants in schizophrenia" (NIH Fellowship 1 F30 MH085467). 12/08 – 11/11; Jon McClellan MD is a mentor for this award (no salary support)
   i) Suleyman Gulsuner, NARSAD Young Investigator Award, Brain and Behavior Research Foundation, "Network analysis in schizophrenia." 01/15 -01/16

11. EDITORIAL RESPONSIBILITIES

1. Editor, Special Section: Research Diagnostic Interviews for the Journal of the American Academy of Child and Adolescent Psychiatry, 1999
2. Editorial Board of the Journal of the American Academy of Child and Adolescent Psychiatry, appointed 1/1/02 to 12/31/04, reappointed 1/1/05 to 12/31/07

12. SPECIAL NATIONAL RESPONSIBILITIES

1) 1989 - 2005: American Academy of Child and Adolescent Psychiatry Committee for Quality Issues, a national committee examining standards of care in the practice of Child Psychiatry.

2) 1990 American Medical Association's Forum on Practice Parameters.

3) 1993 American Psychiatric Association's Work Group on Bipolar Disorder.

4) 1993 Ad Hoc Committee on Facilitated Communication, American Academy of Child and Adolescent Psychiatry.

5) Editorial Board of the Journal of the American Academy of Child and Adolescent Psychiatry, appointed 1/1/02 to 12/31/04, reappointed 1/1/05 – 12/31/07

6) Consensus Conference: Bipolar Disorder Research Forum, sponsored by the American Academy of Child and Adolescent Psychiatry, 2002.

7) Expert Consensus Panel: Management of Antipsychotic Side Effects in Children and Adolescents. Elizabeth Pappadopulos Ph.D. and Peter Jensen, MD. 09/03

8) CBS Evening News with Dan Rather, "Rethinking Bipolar Kid's Treatment." 11/10/03; Interviewed by Mika Brzezinski. http://www.cbsnews.com/news/rethinking-bipolar-kids-treatment/

9) Board of Child Youth and Families, The National Academies: Delivering mental health services for children in pediatric and other primary care settings. Invited Presenter, 5/20/04

10) NICHD: National Child Study. Author of White Paper Addressing Develolpmental Psychiatric Assessments

11) "Pharmacologically Treating Behavioral and Emotional Disturbances in Children: Engaging the Controversies". Workshop Sponsored by the Hastings Center

12) NIMH Workshop on Child and Adolescent Onset Schizophrenia, July 2007. Chair of session on genetic and environmental risk factors.

13) CBS "60 Minutes". Interviewed by Katie Couric for an episode examining the controversies surrounding bipolar disorder in children. October, 2007. www.cbsnews.com/videos/what-killed-rebecca-riley/

14) Invited Participant: NIH funded workshops "Pharmacologically treating behavioral and emotional disturbances in Children, Engaging the Controversies". Hastings Center, 2007 – 2009

15) Consultant: GAO review of psychotropic prescriptions for youth in foster care. 2011-2014

16) AACAP. Program Committee for Annual Meeting, 2013 - ongoing

13. SPECIAL LOCAL RESPONSIBILITIES

1) Hospital Committees
   a) Children's Hospital and Regional Medical Center, Child Psychiatry
      i) Clinical Services Committee
      ii) Executive Committee
   b) Child Study and Treatment Center
      i) Executive Committee
      ii) Clinical Services Committee
      iii) Quality Improvement Committee

2) Mental Health Issue Study Group, a committee organized to develop a mental health benefits package for the Washington State Health Commission, to be instituted as part of the State's Uniform Benefit's Package 1993

3) Co-chair, Re-engineering Committee for Psychosocial Services, Children's Hospital and Medical Center, 1995

4) Committee to Review Psychotherapy Training, Department of Psychiatry, University of Washington, 1996

5) Institutional Review Board, Department of Social and Health Services, Washington State, 1998 - 2000

6) Washington State Advisory Board for the Review of Child Deaths in Institutional Settings, 1999 - 2001

7) Promotions Committee, Department of Psychiatry, University of Washington, 1999 - 2001

8) Washington State Council Child and Adolescent Psychiatry, Secretary on the Executive Committee. 2000 – 2001

9) Institutional Review Board, Children's Hospital and Regional Medical Center, Seattle, WA 2000 – present

10) Committee to Review Year 2 Residency Didactics, University of Washington Department of Psychiatry, 2001

11) Washington State Council Child and Adolescent Psychiatry, President of the Executive Committee, 2001 – 2003

12) Pediatric Scientific Advisory Committee, Children's Hospital and Regional Medical Center, Seattle, WA, 2002

13) Clinical Research Steering Committee, Children's Hospital and Regional Medical Center, Seattle, WA, 2004

14) Children's Mental Health Steering Committee: requested by Department of Health and Social Services, Washington State, 2005

14. RESEARCH FUNDING

GRANTS:

1) 1990: "Early Onset Psychotic Disorders," Primary Investigator: Jon McClellan, MD. Funded through the Washington State Institute for Mental Health Research and Training. Awarded $1,600.

2) 1991: "Language Disturbances in Chronically Mentally Ill Adolescents," Primary Investigator: Jon McClellan, MD. Funded through the Washington State Institute for Mental Health Research and Training. Awarded $14,000.

3) 1994 - 2000: NIMH K20 Award. "Early Onset Schizophrenia," (K20 MH01120) Primary Investigator: Jon McClellan, MD. Awarded $645,456 (total direct costs).

4) 2000 – 2005: NIMH R01 grant "Familial Psychiatric Disorders and Attention in Schizophrenia" (MH45112) PI: Robert Asarnow, Ph.D., UCLA, with a subcontract with the University of Washington, Jon McClellan, M.D. Specific Aims: To examine for the genetic correlates of either diagnosis or neuropsychological functioning in families of youth with early onset schizophrenia.

5) The Genetics of Schizophrenia. PI: Jon McClellan, MD. 7/1/00 – 6/30/01. Funded by the Washington Institute of Mental Health ($50,000). Role: Primary Investigator, 20% effort. Creating a DNA library from adult patients with schizophrenia.

6) NIH K23 Grant Award - Mentored Patient-Oriented Research Career Development Award, PI: Wendy Weber, "Controlled Trial of Hypericum for Juvenile Depression." (5K23AT000929). Funding period: 4/1/02 to 3/31/07, Role: mentor.

7) Treatment of Early Onset Schizophrenia and Schizoaffective Disorder. NIMH U-01, MH61464-01A1, PI: Jon McClellan, MD, 9/01 – 8/07. Total direct costs are $1,150,000 for the UW site. A multi-site study (University of Washington, University of North Carolina, Case Western and Harvard) comparing the atypical antipsychotic agents risperidone and olanzapine to molindone, a typical neuroleptic, in youth with schizophrenia and schizoaffective disorder.

8) NIH K23 Grant Award – Mentored Patient-Oriented Research Career Development Award, PI: Stefanie Hlastala, "Interpersonal and Social Rhythm Therapy for Adolescents with Bipolar Disorder." (1K23MH070570). Funding period is 1/1/05 - 1/1/10. Jon McClellan MD is a mentor for this award (no salary support)

9) Efficacy and Tolerability of Ziprasidone in Children and Adolescents with Schizophrenia Spectrum Disorders. Pfizer, PI: Jon McClellan MD, 9/03 – 6/06. Total Costs: $140,000, An open label trial of ziprasidone in youth with schizophrenia spectrum disorders.

10) Pharmacogenetics of Early Schizophrenia, Stanley Medical Research Institute. PI: Jon McClellan MD. 9/02 – 9/07: 5 % effort. Total direct costs 265,500. This proposal provides funds to create cell lines and perform preliminary genetic analyses, using subjects and data from the study "Treatment of Early Onset Schizophrenia and Schizoaffective Disorder."

11) Best Pharmaceuticals for Children Act Pediatric Off-Patent Drug Study (PODS): Lithium for the Treatment of Pediatric Mania. NICHD HHSN275200503406C, PI: Robert Findling, Case Western. Project Aims: Establish the safety and efficacy for pediatric mania. This is a multi-site trial, Jon McClellan MD is the PI of the UW site. Total direct costs at UW site: $1,184,454. Project Period: 9/30/2005 – 5/1/2011.

12) A Genomic Approach to Gene Discovery in Schizophrenia, PI: Mary Claire King, Ph.D., National Alliance for Research in Schizophrenia and Depression (NARSAD), $100,000. Project Aims: Use ROMA technology to identify *de novo* deletions or duplications in individuals with sporadic cases of schizophrenia. Project Period: 6/1/06 – 6/1/08

13) NIH Fellowship Award, PI: Diane Dickel, predoctoral student, Department of Genetics: "A Genomic Approach to Studying Repeat Instability in Schizophrenia" (NIH Fellowship 1 F31 MH081509). 7/07 – 6/12; Jon McClellan MD is a mentor for this award (no salary support)

14) Characterization of a brain specific mRNA disrupted by inherited translocation in a young schizophrenia patient, PI: Tom Walsh, Ph.D., Research Assistant Professor, Division of Medical Genetics, University of Washington, NARSAD Young Investigator Award, $30,000, 6/07 – 6/09, Jon McClellan MD is a mentor for this award (no salary support).

15) NIH Fellowship Award, PI: Cait Rippey, MSTP student, Department of Medicine: "Rare structural genomic variants in schizophrenia" (NIH Fellowship 1 F30 MH085467). 12/08 – 1/11; Jon McClellan MD is a mentor for this award (no salary support)

16) MH083989 Rare Copy Number Variants in Schizophrenia, Co-PIs: Mary Claire King, Jon McClellan, Tom Walsh. Use genome-wide screening tools to detect rare copy number variants in samples collected from three large collaborative NIH funded multisite studies: 1) The Genetics of Endophenotypes and Schizophrenia; 2) Schizophrenia Liability Genes among African Americans; and 3) A Neurobehavioral Family Study of Schizophrenia. Total Direct Costs ~ 5,000,000, 1/09 – 12/14

17) MH096844 Genomics of Schizophrenia in the South African Xhosa. Co-PIs: Mary Claire King, Jon McClellan, Tom Walsh. Use exome sequencing to detect genes important for schizophrenia in the Xhosa, an ancient population of South Africa. Total direct costs ~ 3,500,000, 1/13 – 12/18.

18) NARSAD Young Investigator Award, PI: Suleyman Gulsuner. "Network analysis in schizophrenia." Funded by the Brain and Behavior Research Foundation 01/15-01/16. Jon McClellan MD is a mentor for this award (no salary support)

OTHER FUNDING:

Child Study Treatment Center Biennial Contract: current contract $2,100,000 total direct Contract has been renewed every two years since 1989.

15. BIBLIOGRAPHY

Manuscripts in Peer Reviewed Journals

1. Cowley, D.S., Dager, S.R., McClellan, J.M., Roy-Byrne, P.P., & Dunner, D.L. Response to Lactate Infusion in Generalized Anxiety Disorder. ***Biological Psychiatry***, 24:409-414, 1987

2. McClellan, J.M. & Trupin, E. Prevention of Psychiatric Disorders in Children, ***Hospital and Community Psychiatry***, 40: 630-636, 1989

3. McClellan, J., Reichler, R., Rupert, M., & Sylvester, C. Attention deficit disorder in children at-risk for anxiety and depression**.** ***Journal of the American Academy of Child and Adolescent Psychiatry***, 29: 534-539, 1990

4. Werry, J.S., McClellan, J., & Chard, L. Child and Adolescent Schizophrenic, Bipolar and Schizo-affective Disorders: A clinical and outcome study**.** ***Journal of the American Academy of Child and Adolescent Psychiatry***, 30: 457-465, 1991

5. Werry, J. & McClellan, J. Predicting Outcome in Child and Adolescent Schizophrenia and Bipolar Disorder. ***Journal of the American Academy of Child and Adolescent Psychiatry***, 31: 147-150, 1992.

6. Trupin, E., Tarico, V., Low, B., Jemelka, R., & McClellan, J. Children on Child Protective Service Caseloads: Prevalence and Nature of Serious Emotional Disturbance. ***International Journal of Child Abuse and Neglect***, 17: 345-388, 1992

7. McClellan, J. and Werry, J.: Schizophrenia. ***Psychiatric Clinics of North America***, 15:131-148, 1992

8. McClellan, J., Werry, J., & Ham, M. A Follow-up Study of Early Onset Psychosis: Comparison between Outcome Diagnoses of Schizophrenia, Mood Disorders and Personality Disorders. ***J. Autism and Developmental Disorders***, 23: 243-262, 1993

9. Werry, J.S., McClellan, J., Ham, M., & Chard, L. Early Onset Schizophrenia. ***Schizophrenia Bulletin***, 20: 619-629, 1994

10. McClellan, J. & Werry, J. Practice Parameters for the Assessment and Treatment of Schizophrenia in Children and Adolescents. ***Journal of the American Academy of Child and Adolescent Psychiatry***, 33: 616-635, 1994; republished in ***Supplement to the Journal of the American Academy of Child and Adolescent Psychiatry***, 36: 157-176S, 1997

11. American Psychiatric Association, Practice Guidelines for the Treatment of Patients with Bipolar Disorder. Primary Authors: Hirschfeld, R., Clayton, P., Cohen, I., Fawcett, J., Keck, P.,

McClellan, J., McElroy, S., Post, R., & Satloff, A. ***Supplement to the American Journal of Psychiatry***, 151: 1-36, 1994

12. Adams, J., McClellan, J., Douglass, D., McCurry, C. & Storck, M. Sexually Inappropriate Behaviors in Seriously Mentally Ill Children and Adolescents. ***Child Abuse and Neglect***, 19: 555-568, 1995

13. McClellan, J., Adams, J., Douglass, D., McCurry, L., & Storck, M. Clinical Characteristics Related to Severity of Sexual Abuse: A Study of Seriously Mentally Ill Youth. ***Child Abuse and Neglect***, 19: 1245-1254, 1995

14. Peterson, S.E., Myers, K.M., McClellan, J., & Crow, S. Neuroleptic Malignant Syndrome: Three Adolescents with Complicated Courses. ***Journal of Child and Adolescent Psychopharmacology***, 5: 139-149, 1995

15. McClellan, J. & Werry, J. Practice Parameter for the Assessment and Treatment of Children and Adolescents with Bipolar Disorder. ***Journal of the American Academy of Child and Adolescent Psychiatry***, 36: 138-156, 1997; republished in ***Supplement to the Journal of the American Academy of Child and Adolescent Psychiatry***, 36: 157-176S, 1997

16. McClellan, J., McCurry, C., Ronnei, M., Adams, J., Eisner, A., & Storck, M. Age of Onset of Sexual Abuse: Relationship to Sexually Inappropriate Behaviors. ***Journal of the American Academy of Child and Adolescent Psychiatry***, 35(10): 1735-1783, 1996.

17. Varley, C. & McClellan, J. Reports of Two Additional Sudden Deaths in Children Receiving Tricyclic Antidepressants. ***Journal of the American Academy of Child and Adolescent Psychiatry***, 36: 390-394, 1997

18. McClellan, J., McCurry, C., Ronnei, M., Adams, J., Storck, M, Eisner, A., & Smith, C. The Relationship between Sexual Abuse, Gender, and Sexually Inappropriate Behaviors. ***Journal of the American Academy of Child and Adolescent Psychiatry***, 36: 959-965, 1997

19. McCurry, C., McClellan, J., Adams, J., Ronnei, M., Storck, M., Eisner, A, Breiger, D. Sexual behavior associated with low Verbal IQ in youth who have severe mental illness. ***Mental Retardation***, February, 36: 23 - 30, 1998

20. McClellan J and McCurry, C. Neurocognitive Pathways in the Development of Schizophrenia. ***Seminars in Clinical Neuropsychiatry***, 3: 320 - 332, 1998

21. McClellan, J. & McCurry, C. Early onset psychotic disorders: Diagnostic stability and clinical characteristics. ***European Child and Adolescent Psychiatry***, 8(Suppl.2), 1-7, 1999

22. Speltz, M, McClellan, J, Deklyen, M, Jones K, Preschool Boys with Oppositional Defiant Disorder: Clinical Presentation and Diagnostic Change over a Two-Year Period. ***Journal of the American Academy of Child and Adolescent Psychiatry***. 38:838-846, 1999

23. McClellan, J, McCurry, C, Snell, J. DuBose, A. Early Onset Psychotic Disorders: Course and Outcome over a Two-Year Period. ***Journal of the American Academy of Child and Adolescent Psychiatry***, 38:1380 – 1389, 1999

24. McClellan J, Werry, J. Introduction--research psychiatric diagnostic interviews for children and adolescents. ***J Am Acad Child Adolesc Psychiatry***. 39:19-27, 2000

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27. AACAP official action. Summary of the practice parameters for the assessment and treatment of children and adolescents with schizophrenia. American Academy of Child and Adolescent Psychiatry. ***J Am Acad Child Adolesc Psychiatry***. 39: 1580-2, 2000

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29. McClellan, J, McCurry, C, Speltz ML, Jones K, Symptom Factors in Early Onset Psychotic Disorders. ***Journal of the American Academy of Child and Adolescent Psychiatry***, 41: 791-798, 2002

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32. McClellan J Breiger D, McCurry, C. Hlaslala S, Premorbid Functioning in Early Onset Psychotic Disorders, ***Journal of the American Academy of Child and Adolescent Psychiatry***, 42:666-672, 2003

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24. McClellan J. Members Forum, Bipolar Disorder Practice Parameters, Annual Meeting of the American Academy of Child and Adolescent Psychiatry, October, 2004, Washington D.C.

25. McClellan J. Early Onset Schizophrenia. Child Welfare League of America, Washington DC, March 2005

26. McClellan J. Evidence Based Care in Child Psychiatry, Psychiatry Grand Rounds, University of Cincinnati Department of Psychiatry, May 2005

27. McClellan J. Practice Parameters for Bipolar Disorder. Annual Meeting of the American Academy of Child and Adolescent Psychiatry, October, 2005, Toronto, Canada

28. McClellan J. Pediactric Bipolar Disorder, Current Controversies. Psychiatry Grand Rounds, University of Arizona, March, 2006, Tucson, Arizona.

29. McClellan J. Genomics of Schizophrenia. Child Psychiatry Grand Rounds, University of Washington, May, 2006

30. McClellan J. Treatment of Early Onset Schizophrenia and Schizoaffective Disorder: Baseline Characteristics. Annual Meeting of the American Academy of Child and Adolescent Psychiatry, October, 2006, San Diego, CA.

31. McClellan J. Schizophrenia: A Rare Allele Model. Early Onset Schizophrenia Symposia, NIH, Bethesda MD. June, 2007

32. McClellan J. Treatment of Early Onset Schizophrenia and Schizoaffective Disorder. Child Psychiatry Grand Rounds. Northwestern University, September 2007

33. McClellan J. TEOSS: Maintenance Therapy. Annual Meeting of the American Academy of Child and Adolescent Psychiatry, October, 2007, Boston, MA

34. McClellan J. Discussant: Symposia on Monitoring Pediatric Psychopharmacology, Annual Meeting of the American Academy of Child and Adolescent Psychiatry, October 2008, Chicago, IL.

35. McClellan J. Rare Alleles and Schizophrenia. Annual Meeting of the American Academy of Child and Adolescent Psychiatry, October 2009, Honolulu, HI.

36. McClellan J. Pediatric Bipolar Disorder, Fact or Fiction. William Friedrich Ph.D. Memorial Lecture, Department of Psychiatry and Psychology, Mayo Clinic, November, 2009, Rochester, MN

37. McClellan J. Rare Alleles and Schizophrenia. World Congress of Psychiatric Genetics, November 2009, San Diego, CA.

38. McClellan J. Rare variants and child psychiatric disorders. Annual meeting of the American Academy of Child and Adolescent Psychiatry, October 2010, New York, NY.

39. McClellan J. U.S. Government Accountability Office. HHS Guidance Could Help States Improve Oversight of Psychotropic Prescriptions. Senate Subcommittee Hearing, Senator Tom Carper Chair, Washington DC, November, 2011

40. McClellan J. Rare variants and child psychiatric disorders. Grand Rounds, Boston Children's Hospital, January, 2012

41. McClellan J. Early Onset Schizophrenia. Grant Rounds, University of Texas Department of Child Psychiatry, Houston, TX February, 2013.

42. McClellan J. Psychotropic Medication Use for Youth in Foster Care. A Forum on Child Welfare, hosted by the Congressional Caucus on Foster Youth. Seattle, WA, May, 2013.

43. McClellan J. Integrating public sector and academic child psychiatry in a state hospital setting. AACAP, San Antonio, Tx. October, 2015.

44. McClellan J. De novo mutations in schizophrenia. American College of Neuropsychopharmacology, Hollywood, Fl. December, 2015

Washington State Health Care Authority

Agency medical director comments

Pharmacogenomics for behavioral health conditions

Charissa Fotinos, MD, MSc
Deputy Chief Medical Officer
Washington State Health Care Authority
January 20, 2017

Background – Conditions of focus

- Depressive disorders
- Schizophrenia spectrum and other psychotic disorders
- Anxiety disorders
- Bipolar and related disorders
- Attention deficit/hyperactivity disorder
- Substance use disorders

2

Agency Medical Director Concerns

Safety = Low

Efficacy = High

Cost = Medium/ High

3

A refresher

Drug metabolism relates to:

- Pharmacokinetics: study or description of the time course of absorption, distribution, metabolism and excretion
- Pharmacodynamics: relationship between the drug concentration at the site of action and the resultant effect, including time, intensity of effect and adverse reactions
- Other factors influencing drug effects are variations in:
  - Absorption
  - Distribution
  - Ability to metabolize and eliminate (genetics)
  - Disease states
  - Drug Interactions

4

Background, cont.

Potential benefits of pharmacogenomics testing largely focus on 3 ideas:

- Early identification of side effects will improve adherence
- Predicting slow or rapid metabolizers of certain drugs may lead to more appropriate dose or medication choice
- The ability to predict the development of serious adverse effects will lead to less harm
- Presupposes alternate, equally effective treatments exist if the risk of an adverse event, (weight gain with an antipsychotic) is elevated

5

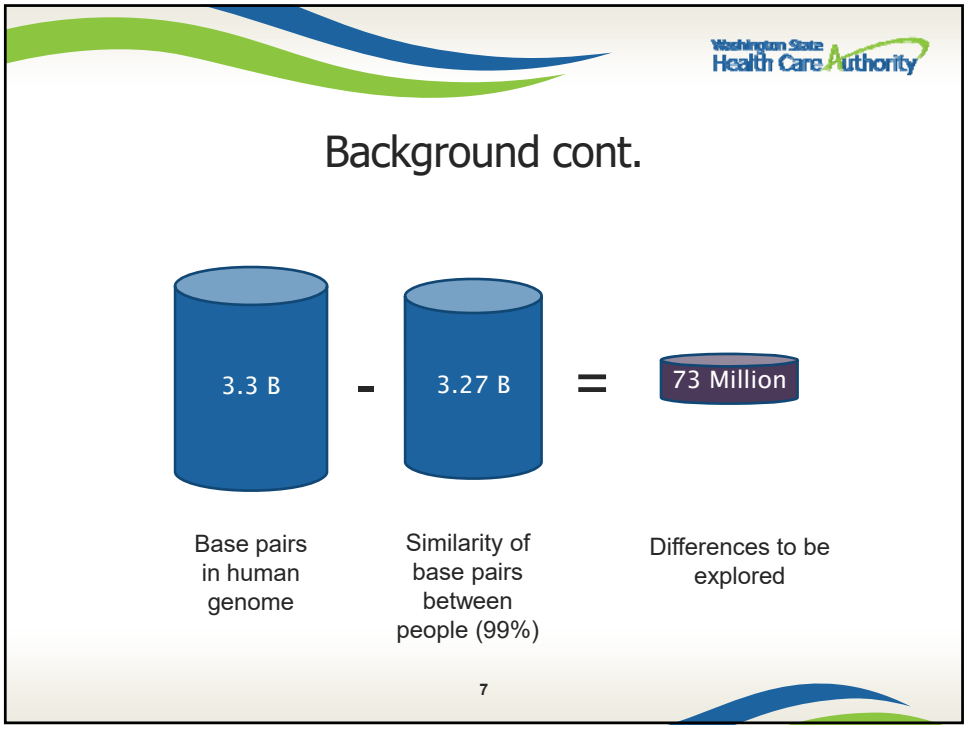
Background, cont.

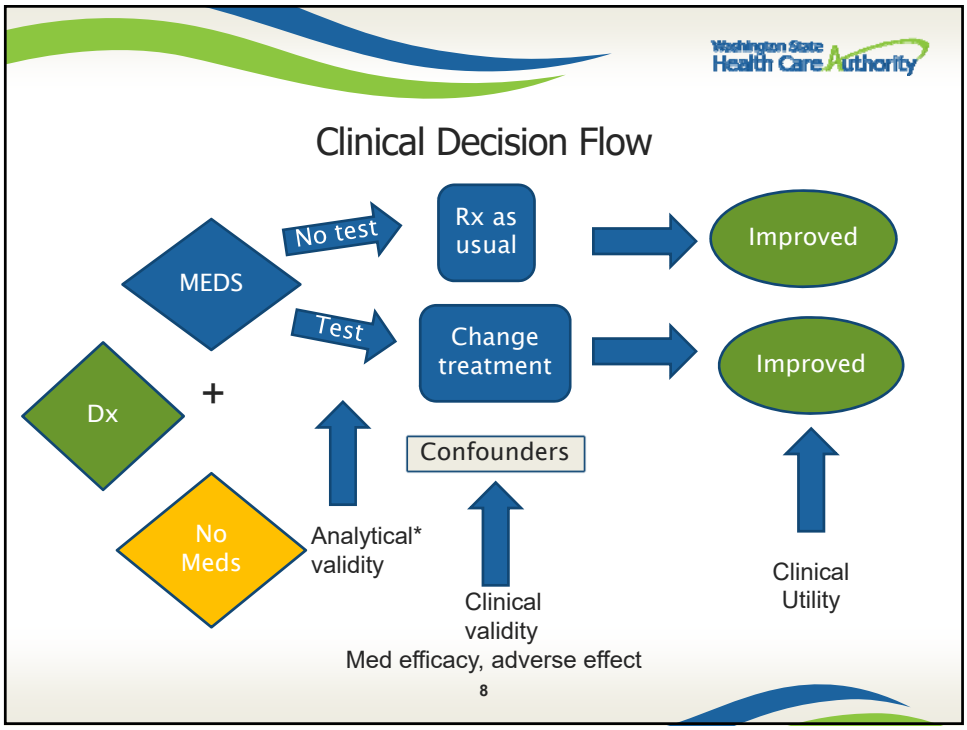
- Additional Considerations:
  - What are the frequencies of the various types of metabolizers?
  - Ex. CYP2D6 (codeine, hydrocodone, oxycodone, tramadol*)
    - 3% of AA, 1-10% of Caucasians and 16-28% of N. African and Ethiopians are Ultrarapid metabolizer
      - Ex. children receiving codeine after a tonsillectomy for sleep apnea
    - 10% of Caucasians and 1% of persons of Asian descent are poor metabolizers

*all of these are pro-drugs

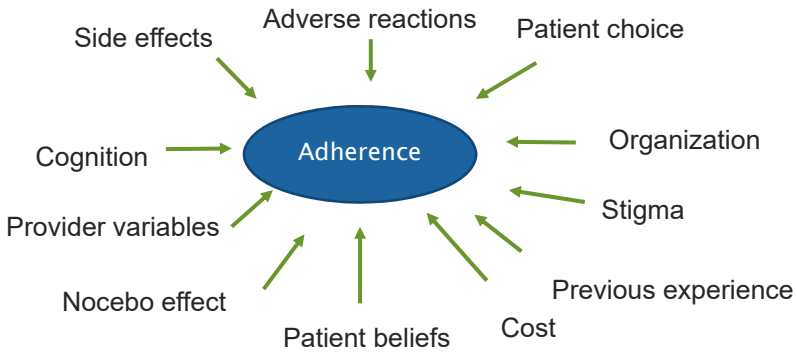
Pharmacogenetic Testing and Opioids
Tennille Collins, PharmD Candidate; Diane Nykamp, PharmD
US Pharmacist. 2015;40(3):23-26.

6


Washington State Health Care Authority
Background cont.
3.3 B
-
3.27 B
=
73 Million
Base pairs in human genome
Similarity of base pairs between people (99%)
Differences to be explored
7


Washington State Health Care Authority
Clinical Decision Flow
MEDS
No test
Rx as usual
Improved
Test
Change treatment
Improved
Dx
+
Confounders
No Meds
Analytical* validity
Clinical validity
Med efficacy, adverse effect
Clinical Utility
8

Background cont.



9

Business is booming

https://genesight.com/

"The GeneSight test is a clinically proven, genetic-based decision support tool that can help get patients on the right medication faster".

http://www.affiliatedgenetics.com/pharmarisk/

"Pharmacogenetics (PGx) is a well-established science studying how an individual metabolizes medications. PharmaRisk® PGx testing provides individualized insight into complex treatment scenarios".

http://www.admerahealth.com/pgx/

"PGxOne™ Plus comprehensively screens 50 well-established pharmacogenomic genes in a single, cost-effective test that provides medically actionable and clinically relevant data, thus allowing physicians to make effective treatment decisions".

10

Considerations in Evaluating Genetic Tests of Association

- Assess the risk for bias
  - Correct definition and accurate recording of phenotype with blinding
  - Have potential differences between diseased and non-diseased been considered? (ethnicity)
  - Measurement of the variants unbiased and accurate
  - Do the genotype proportions observe the Hardy-Weinberg equilibrium?
  - Have the inferences been adjusted for multiple comparisons?
  - Are the results consistent with other studies?
- How large and precise are the results?
- Can the results be applied to patient care?
  - What are the absolute and relative effects?
  - Is the patient better off as a result?
  - Is the risk associated allele likely to be present in my patient?

User's Guide to the Medical Literature: 3rd Edition

Current State Agency Policy

PEBB	Not covered; Investigational
Medicaid FFS and Managed Care	Not covered; Covered–criteria not known
Labor and Industries	Not covered
Dept. of Corrections	Covered; Requires PA

12

Gene Tests Performed

Drug	Indication(s)/Therapeutic Area (class)	Associated Gene	CPT Code
Clobazam	Neurology/Narrow-Spectrum AED	CYP2C19	81225
Diazepam	Psychiatry/Anti-anxiety/Narrow-Spectrum AED	CYP2C19	81225
Doxepin	Psychiatry/Antidepressant (TCA)	CYP2C19, CYP2D6	81225, 81226
Amitriptyline	Psychiatry/Antidepressant (TCA)	CYP2D6	81226
Aripiprazole	Psychiatry/Atypical antipsychotic	CYP2D6	81226
Clomipramine	Psychiatry/Antidepressant (TCA)	CYP2D6	81226
Clozapine	Psychiatry/Atypical antipsychotic	CYP2D6	81226
Desipramine	Psychiatry/Antidepressant (TCA)	CYP2D6	81226
Fluoxetine	Psychiatry/Antidepressant (SSRI)	CYP2D6	81226
Fluvoxamine	Psychiatry/Antidepressant (SSRI)	CYP2D6	81226
Iloperidone	Psychiatry/Atypical antipsychotic	CYP2D6	81226
Imipramine	Psychiatry/Antidepressant (TCA)	CYP2D6	81226
Modafinil	Psychiatry/Psycho-stimulant (promote wakefulness)	CYP2D6	81226
Nefazodone	Psychiatry/Antidepressant* (5-HT2A receptor antagonist)	CYP2D6	81226

13

Gene Tests Performed

Drug	Indication(s)/Therapeutic Area (class)	Associated Gene	CPT Code
Nortriptyline	Psychiatry/Antidepressant (TCA)	CYP2D6	81226
Paroxetine	Psychiatry/Antidepressant (SSRI)	CYP2D6	81226
Perphenazine	Psychiatry/Antipsychotic (typical)	CYP2D6	81226
Pimozide	Psychiatry/Antipsychotic	CYP2D6	81226
Protriptyline	Psychiatry/Antidepressant (TCA)	CYP2D6	81226
Risperidone	Psychiatry/Atypical antipsychotic	CYP2D6	81226
Thioridazine	Psychiatry/Antipsychotic* (typical)	CYP2D6	81226
Trimipramine	Psychiatry/Antidepressant (TCA)	CYP2D6	81226
Venlafaxine	Psychiatry/Antidepressant (SNRI)	CYP2D6	81226
Vortioxetine	Neurology/Antidepressant (serotonin modulator and stimulator)	CYP2D6	81226
Citalopram	Psychiatry/Antidepressant (SSRI)	CYP2D6, CYP2C19	81226
Carbamazepine	Neurology/ Narrow-Spectrum AED/Bipolar disorder medication	HLA-A, HLA-B	81380
Phenytoin	Neurology/ Narrow-Spectrum AED	HLA-B	81380
Valproic Acid	Neurology/Broad-Spectrum AED	NAGS, CPS1, ASS1, OTC, ASL, ABL2, POLG	80164, 80165

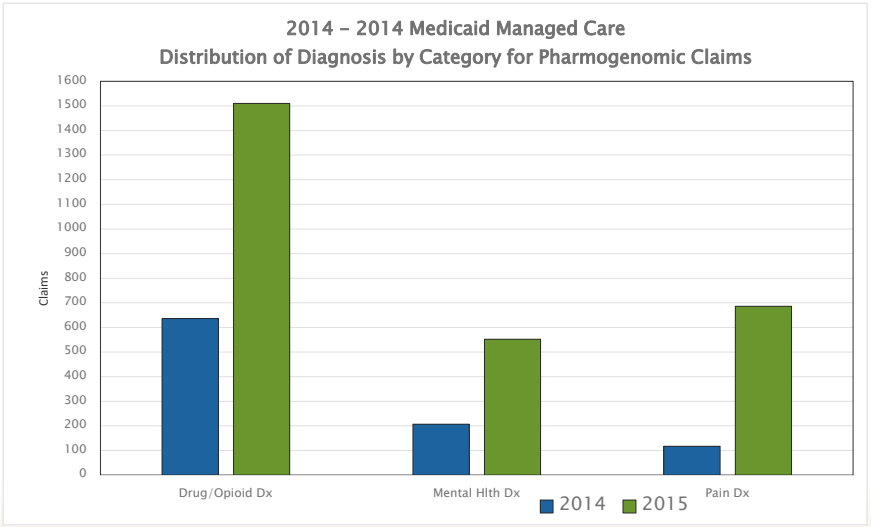
14

Gene tests performed

CPT Code	Test: Gene Specified in Labeling
81225	CYP2C19 (cytochrome P450, family 2, subfamily C, polypeptide 19) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *4, *8, *17)
81226	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *4, *5, *6, *9, *10, *17, *19, *29, *35, *41, *1XN, *2XN, *4XN)
81227	CYP2C9 (cytochrome P450, family 2, subfamily C, polypeptide 9) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *5, *6)
81479	Unlisted molecular pathology procedure

5

Agency Utilization and Cost Medicaid MCO 2014-2015



16

Agency Utilization and Cost

AGENCY COST AND UTILIZATION – Pharmacogenomic Testing

Unique Members and Procedures

	2013		2014		2015	
	Unique member	Procedure	Unique member	Procedure	Unique member	Procedure
PEBB/UMP	112	152	135	239	80	110
Medicaid MCO	0	0	3,995	6,835	5,566	13,272
Medicaid FFS	0	0	49	55	59	64

Total Paid Dollars by Agency

Measure	2013		2014		2015	
	Paid dollars	Paid/ Procedure	Paid dollars	Paid/ Procedure	Paid dollars	Paid/ Procedure
PEBB/UMP	$8,179	$54	$16,683	$70	$5,480	$50
Medicaid MCO	$0	$0	$1,646,337	$241	$3,149,326	$237
Medicaid FFS	$0	$0	6,940	$112	$12,636	$197

Most Common Pharmacogenomic CPT Codes and Average Paid Dollars 2014 and 2015

	81479	81225	81401	80164
PEBB/UMP	65 ($117)	21 ($128)	24 ($99)	307 ($28)
	81479	81225	81226	81227
Medicaid MCO	2,379 ($298)	1,552 ($236)	1,539 ($365)	905 ($140)

17

Key Questions

1. Effectiveness: What is the clinical utility of genetic testing to inform the selection or dose of medications for individuals diagnosed with depression, mood disorder, psychosis, anxiety, attention deficit/hyperactivity disorder (ADHS), or substance use disorder?
   a. Does genetic testing to inform the selection or dose of medications change the drug or dose selected by physicians and/or patients compared with usual care/no genetic testing?
   b. Do decisions about selection or dose of medications guided by genetic testing result in clinically meaningful improvement in patient response to treatment or reduction in adverse events as a result of treatment compared with decisions based on usual care/no genetic testing?
2. Harms: What direct harms are associated with conducting genetic testing when it is use to inform the selection or dose of medication?

18

Key Questions

3. Special populations: Compared with usual care/no genetic testing, do decision making, patient outcomes, or harms following genetic testing to inform the selection or dose of medications vary by:

   a. Clinical history (e.g., prior treatment, whether the diagnosis is initial or recurrent, duration of diagnosis, severity of illness, or concurrent medications); or
   b. Patient characteristics (e.g., such as age, sex or comorbidities)?

4. Costs: What are the costs and cost-effectiveness of genetic testing to guide the selection or dose of medications?

19

Effectiveness

Question	Quality of evidence	Findings
Dose or med change compared to no test?	Low	Might change behavior
Are remission rates improved?	Low	Might improve rates but clinical significance not shown
Are response rates improved?	Low	Suggests improvement
Improved adherence, tolerance, fewer adverse events?	Very low	Suggests improvement

20

Effectiveness

Question	Quality of evidence	Findings
Are there any direct harms?	No direct evidence found	NA
Sub group differences related to clinical history?	Insufficient evidence found	NA
Sub group differences related to patient characteristics?	Insufficient evidence found	NA
Cost comparison, effectiveness and utility studies?	Variable methodology and quality	Indeterminate

21

National Coverage Decision (NCD)

- CMS: No National Coverage Decision
- Noridian:
  - Allows psychiatrist/neuropsychiatrists to use GeneSight® Psychotropic for refractory depression with treatment failure
  - Testing for CYP2D6 allowed when using amitriptyline or nortriptyline for the treatment of depressive disorders
  - Testing for HLA-B*15:02 when carbamazepine use being considered for use in persons of Asian or Oceanic descent

22

Agency medical director recommendations for pharmacogenomic testing

- **Depressive disorders**: Do not cover
- **Schizophrenia spectrum and other psychotic disorders**: Do not cover
- **Anxiety disorders**: Do not cover
- **Bipolar and related disorders**:
  - Cover only **HLA-B*15:02, (CPT 81380)** in persons of Asian and Oceanic descent in whom carbamazepine use is being considered (The FDA label lists as required.)
- **Attention deficit/hyperactivity disorder**: Do not cover
- **Substance use disorders:** Do not cover

23

Questions?

More Information:
www.hca.wa.gov/about-hca/health-technology-assessment/pharmacogenomic-testing-selected-conditions

24

Washington State Health Care Authority

Order of scheduled presentations:

Pharmacogenomic testing for selected conditions

	Name
1	Jim Pollard, National Account Manager Government Accounts, Assurex Health
2	Nathan Roe, PhD, Medical Science Liasion, Assurex Health

Disclosure

Any unmarked topic will be considered a "Yes"

	Potential Conflict Type	Yes	No
1.	Salary or payments such as consulting fees or honoraria in excess of $10,000.	X	
2.	Equity interests such as stocks, stock options or other ownership interests.		X
3.	Status or position as an officer, board member, trustee, owner.		X
4.	Loan or intellectual property rights.		X
5.	Research funding.		X
6.	Any other relationship, including travel arrangements.		X

If yes, list name of organizations that relationship(s) are with and for #6, describe other relationship:

Assurex Health

	Potential Conflict Type	Yes	No
7.	Representation: if representing a person or organization, include the name and funding sources (e.g. member dues, governmental/taxes, commercial products or services, grants from industry or government).		X

If yes to #7, provide name and funding Sources: _____

*If you believe that you do not have a conflict, but are concerned that it may appear that you do, you may **attach additional sheets** explaining why you believe that you should not be excluded.*

I certify that I have read and understand this Conflict of Interest form and that the information I have provided is true, complete, and correct as of this date.

X [redacted] 1/5/17

Signature *Date*

Nathan Roe

Print Name

So we may contact you regarding your presentation, please provide the following:

Email Address: nroe@assurexhealth.com

Phone Number: 425-772-1207

Disclosure

Any unmarked topic will be considered a "Yes"

	Potential Conflict Type	Yes	No
1.	Salary or payments such as consulting fees or honoraria in excess of $10,000.		X
2.	Equity interests such as stocks, stock options or other ownership interests.		X
3.	Status or position as an officer, board member, trustee, owner. (employee)	X	
4.	Loan or intellectual property rights.		X
5.	Research funding.		X
6.	Any other relationship, including travel arrangements.		X

If yes, list name of organizations that relationship(s) are with and for #6, describe other relationship:

	Potential Conflict Type	Yes	No
7.	Representation: if representing a person or organization, include the name and funding sources (e.g. member dues, governmental/taxes, commercial products or services, grants from industry or government).		X

If yes to #7, provide name and funding Sources:

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I certify that I have read and understand this Conflict of Interest form and that the information I have provided is true, complete, and correct as of this date.

X [redacted] 1-5-17

Signature *Date*

James Pollard

Print Name

So we may contact you regarding your presentation, please provide the following:

Email Address: JPollard@assurehealth.com

Phone Number: 513-701-5048

GeneSight® Psychotropic; Clinical Validity, Utility and Health Economics

Nathan Roe, PhD
Medical Science Liaison

genesight®

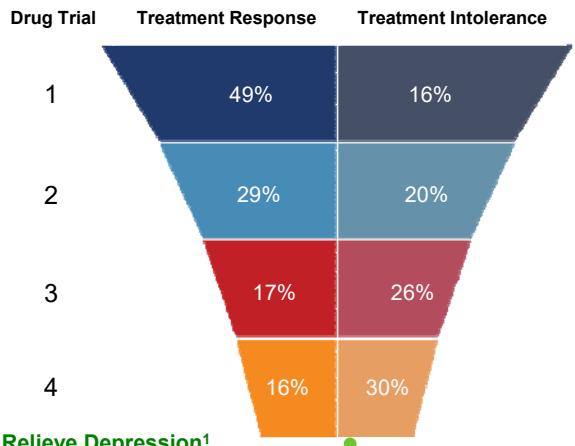
assurex health

Current Standard of Care

"The effectiveness of antidepressant medications is generally comparable between classes and within classes of medications." – American Psychiatric Association

Current Prescribing Practice is Highly Empiric

- Repeated drug trials with limited efficacy
- Increasing rates of side effects
- 70% non-compliance
- High rates of polypharmacy



Sequenced Treatment Alternatives to Relieve Depression[1]

Warden D , et all. The STAR*D project results: a comprehensive review of findings. Current Psychiatry Reports. 2007:9:449-459

genesight®

GeneSight Key Differentiators

Only psychiatric pharmacogenomic test with a positive local coverage determination (LCD) from CMS, effective October 24, 2014

Only patented Combinatorial Pharmacogenomic (CPGx™) test for mental illness

Only test with 5 completed and published clinical trials proving clinical validity, clinical utility and cost effectiveness

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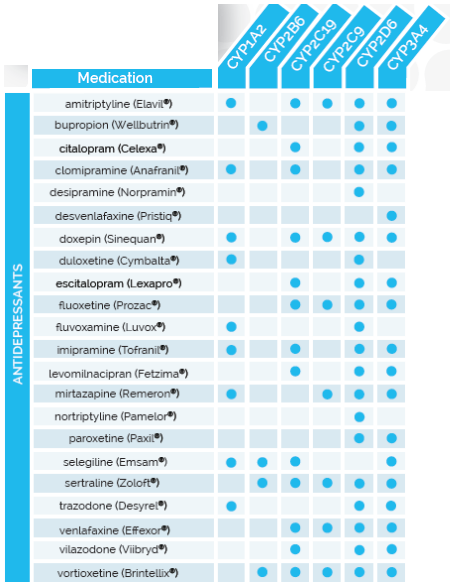
Antidepressant Pharmacokinetics



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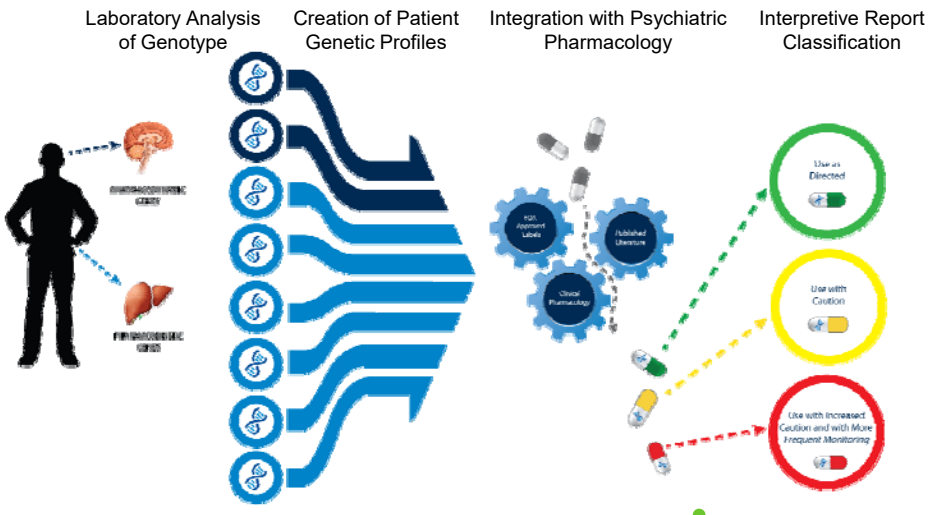
GeneSight Pharmacogenomic Data Integration

GeneSight Psychotropic

Pharmacodynamic (PD)
SLC6A4
(serotonin transporter)

5HTR2A
(serotonin 2A receptor)

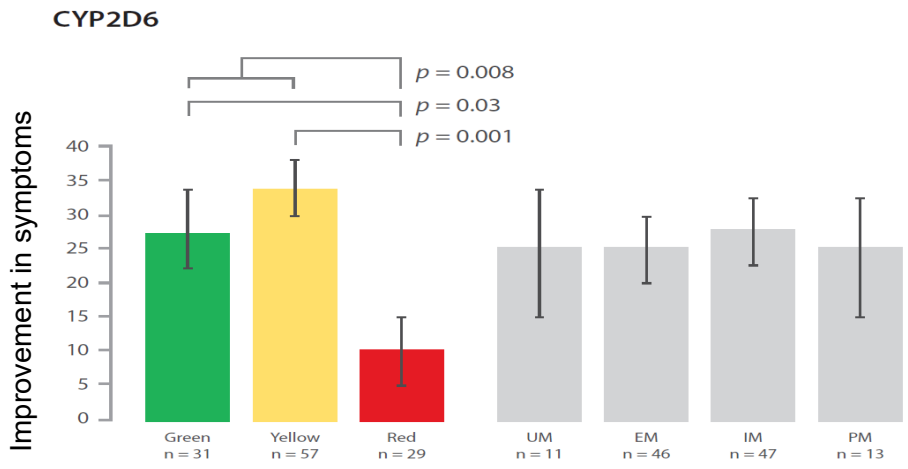
Pharmacokinetic (PK)
CYP2D6
CYP2C19
CYP2C9
CYP1A2
CYP2B6
CYP3A4



>20,000 Patient Genetic Profiles

genesight

Multi-gene vs Individual-gene Analyses



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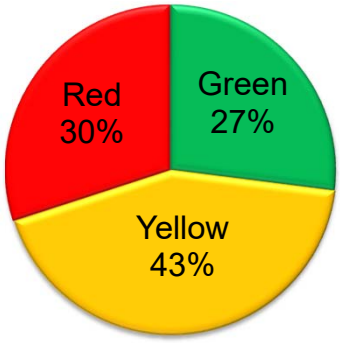
Clinical Validity – Pine Rest RCT

In the Pine Rest study, 30% of patients were taking red-category medications at baseline.



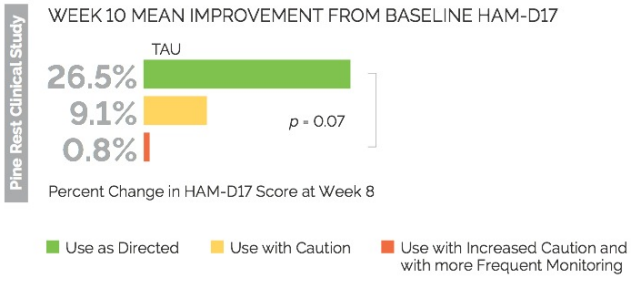
<u>Thirty percent</u> of the patients in a typical psychiatric practice are taking red-category medications, unbeknownst to their treating clinician.

Winner JG, et al. A prospective, randomized double-blind study assessing the clinical impact of integrated pharmacogenomic testing for major depressive disorder. Discovery Med 2013. 16(89): 219-227.

genesight

Clinical Validity – Pine Rest RCT

The Pine Rest Study was a blinded, randomized controlled trial of 49 subjects with a primary diagnosis of a major depressive disorder. The study compared 10 weeks of treatment guided by GeneSight with unguided TAU.



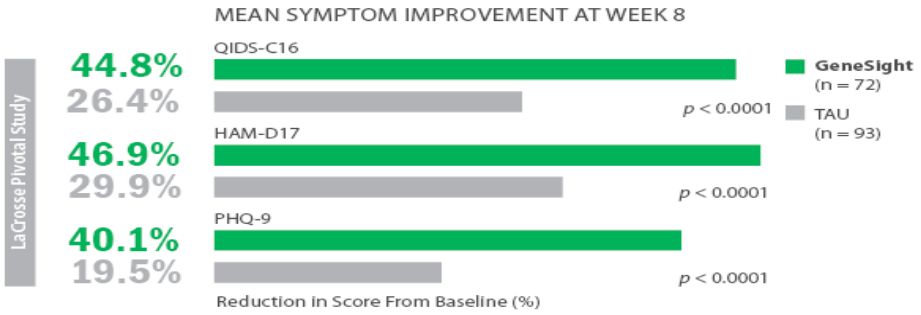
*TAU patients who began the trial on red-category medications **showed almost no improvement.***

Winner JG, et al. A prospective, randomized double-blind study assessing the clinical impact of integrated pharmacogenomic testing for major depressive disorder. Discovery Med 2013. 16(89): 219-227.

genesight

Phase III – La Crosse Study

The La Crosse Study was a prospective, cohort study of 165 subjects with a primary diagnosis of a major depressive disorder. The study compared 8 weeks of treatment guided by GeneSight with unguided TAU.



Treatment guided by GeneSight resulted in ~70% greater improvement in symptoms

Hall-Flavin DK, et al. Utility of integrated pharmacogenomic testing to support the treatment of major depressive disorder in a psychiatric outpatient setting. Pharmacogenetics & Genomics. 2013 Oct;23(10):535-548.

genesight

Medication Congruence

Clinicians' medication decisions were evaluated for congruence with GeneSight's recommendations.

Patients whose clinicians followed report recommendations saved over $2,700 in total medication costs

Allen JD, et al. GeneSight Psychotropic decreases medication costs in a large, prospective case control project. Poster presented at NEI Psychopharmacology Congress, Colorado Springs, CO. Nov 2014..

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DISCUSSION

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GeneSight vs Wellbutrin Approval

GeneSight Psychotropic		
Trial	Duration	Sample Size
Pine Rest Phase III Study	10 weeks	25 GeneSight v 24 Standard of Care
Hamm Clinic Phase II Study	8 weeks	22 GeneSight v 22 Standard of Care
La Crosse Phase III Study	8 weeks	72 GeneSight v 93 Standard of Care

Wellbutrin (buproprion)		
Trial	Duration	Sample Size
1	4 weeks	48 Wellbutrin (300-600mg) v 27 Placebo
2	4 weeks	34 Wellbutrin (450mg) v 34 Placebo
3	6 weeks	110 Wellbutrin (300mg) v 106 Placebo

Wellbutrin FDA Approved Label

genesight

Pharmacogenomic Testing for Selected Conditions

Margaret A. Piper, PhD, MPH
Candi Wines, MPH
Caitlin Kirkwood, PhD
Belinda Rowland, MS, PhD
Karen Crotty, PhD, MPH

Hayes, Inc.
January 20, 2017

Presentation overview

- Background ✓
- Objectives
- Methods and Search Results
- Findings
- Practice Guidelines and Payer Policies
- Overall Summary and Discussion

2

BACKGROUND – Neuropsychiatric Disorders

- 2014: ~43.6 million adults in the U.S. with a mental illness
  - ~9.8 million adults with serious mental illness
- 2002: Total direct + indirect costs of serious mental illness > $300 billion/year
- Neuropsychiatric disorders accounted for the largest proportion of health-related disability in the U.S.
- In 2008, 13.4% of adults in the U.S. received treatment for a mental health problem

►**Societal burden of mental and behavioral disorders is high**

3

BACKGROUND – Disorders of Interest

- Depressive disorders
- Schizophrenia spectrum and other psychotic disorders
- Anxiety disorders
- Mood disorders (includes bipolar disorder)
- Attention deficit/hyperactivity disorder (ADHD)
- Substance use disorder (opioid and alcohol abuse)

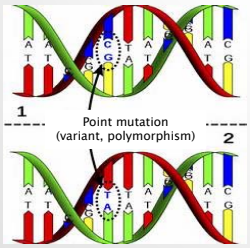
- **IN COMMON:**
  - Multimodal approach to treatment, including medications
  - Medication effectiveness variable; side effects may reduce adherence

4

BACKGROUND – Pharmacogenomics

Pharmacogenomics defines relationships between:

Base sequence variants in genes



Patients likely to respond to specific medications

Patients likely to experience adverse events from specific medications

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BACKGROUND – Pharmacogenomics

- Normal or altered gene products may affect . . .
  - Pharmacokinetics: Drug uptake and metabolism
  - Pharmacodynamics: Target of drug action
- Example: Pharmacokinetics
  - Cytochrome P450 2C19 enzyme metabolizes citalopram, escitalopram, amitriptyline, and sertraline antidepressants
  - Poor metabolizers
    - Patients with *CYP2C19* variants that result in little to no enzyme activity
    - May have ↑ drug exposure with ↑ potential for side effects
  - Ultrarapid metabolizers
    - Patients have extra *CYP2C19* copies that result in ↑ enzyme activity
    - May experience ↓ exposure and ↓ response

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BACKGROUND – Pharmacogenomics

Other sources affecting drug metabolism:

- Metabolic redundancy, e.g., sertraline
  - "The observation that multiple enzymes appear to be involved in sertraline metabolism (CYP2B6, CYP2C19, CYP2C9, CYP3A4, and CYP2D6) suggests that there should be no single agent that could substantially alter the pharmacokinetics of sertraline, nor should there be any single drug-metabolizing enzyme genetic polymorphism that could profoundly impact the pharmacokinetics of sertraline."

    --Obach et al. 2005;33(2):262-270.
- Age
- Gender
- Drug-drug interaction
- Inhibition of specific CYP450 enzymes by specific SSRIs
- Liver, renal, and cardiac function

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BACKGROUND – Diagnostic Test Evaluation

- Clinical validity
  - How well do gene variants predict patient outcomes?
  - MANY studies
    - Estimate association of gene variants and outcomes
    - MANY different variant-outcome combinations
    - See Appendix 1
  - Constitutes the vast majority of PGx evidence
  - ▶Provides the rationale for PGx testing, but not the evidence that it improves patient outcomes

Background

- Clinical utility
  - Does PGx testing change medical decision-making and lead to improved patient outcomes?

Findings (Evidence)

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Background – Clinical Validity

- E.g., Schizophrenia treated with antipsychotic medication

Gene–Outcome Association	# Pts in MA	Odds Ratio (95% CI)	P Value
CYP2D6 genotype and dystonia	195	OR 0.83 (0.38, 1.81)	P=0.64
CYP2D6 genotype and parkinsonism	339	OR 1.64 (1.04, 2.58)	P=0.03
CYP1A2*1F genotype and tardive dyskinesia	386	OR 1.05 (0.50, 2.2)	P=0.89
COMT (val158val) and tardive dyskinesia	NR	OR 1.59	P=0.004
Taq1A in DRD2 and tardive dyskinesia	1528	OR 1.30 (1.03, 1.65)	P=0.026
DRD1 (rs4532) and antipsychotic response	1300	OR 1.17 (0.90, 1.52)	P=0.23

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Combining PGx Predictors: PGx Panels

PGx Panel	Genes Tested	Description of Results
GeneSight Psychotropic (Assurex Health Inc., United States)	*CYP2D6*, *CYP2C19*, *CYP1A2*, *SLC6A4*, *HTR2A(T012C)* (per Winner 2013) *CYP2C9*, *CYP3A4*, *CYP2B6* (website)	Proprietary interpretive report and recommendations in which 26 psychiatric medications are placed in the advisory categories of • "use as directed," • "use with caution," or • "use with caution and more frequent monitoring" based on known pharmacological profile and specific patient genotype
Genecept Assay (Genomind, United States)	*CYP2D6*, *CYP2C19*, *SLC6A4*, *CACNA1C*, *DRD2*, *COMT*, *MTHFR*	Interpretive report lists genetic variants and their individual therapeutic implications; a drug interaction summary categorizes medications as • "use as directed," • "therapeutic options," or • "use with caution"
Neuro-pharmagen (AB Biotics, Spain)	*CYP2D6*, *CYP2C19*, *CYP2C9*, *CYP1A2*, *CYP2B6*, *EPHX1*, *BDNF*, *5-HTTLPR*, *ABCB1*, *GRIK4*, *HTR2C*, *DRD2*-related, *GRIK2*, *GRIA3* and others	A total of 20 genes were tested (Espadaler 2016; 26 now on website); summary and recommendations regarding drug and dose choices based on patient genotype is provided
CNSDose (Australia)	*CYP2D6*, *CYP2C19*, *UGT1A1*, *ABCB1*, *ABCC1*	Interpretive report with recommended antidepressant and dose ranges

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Presentation overview

- Background ✓
- Objectives ✓
- Methods and Search Results
- Findings
- Practice Guidelines and Payer Policies
- Overall Summary and Discussion

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Objectives

- Policy Context
  - Laboratory tests are available to assess patient response to drugs.
  - Potential benefits: Better prescribing choices for the individual patient.
  - Concerns: Tests → improved treatment decisions and patient health outcomes?
- Key Questions

1. Effectiveness: What is the clinical utility of genetic testing to inform the selection or dose of medications for individuals diagnosed with depression, mood disorders, psychosis, anxiety, attention deficit/hyperactivity disorder (ADHD), or substance use disorder?
   a. Does genetic testing to inform the selection or dose of medications change the drug or dose selected by physicians and/or patients compared with usual care/no genetic testing?
   b. Do decisions about selection or dose of medications guided by genetic testing result in clinically meaningful improvement in patient response to treatment or reduction in adverse events as a result of treatment compared with decisions based on usual care/no genetic testing?

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Objectives

- Key Questions (cont'd)

2. Harms: What direct harms are associated with conducting genetic testing when it is used to inform the selection or dose of medications?
3. Special populations: Compared with usual care/no genetic testing, do decision-making, patient outcomes, or harms following genetic testing to inform the selection or dose of medications vary by:
   a. Clinical history (e.g., prior treatments, whether the diagnosis is initial or recurrent, duration of diagnosis, severity of illness, or concurrent medications); or
   b. Patient characteristics (e.g., such as age, sex, or comorbidities)?
4. Costs: What are the costs and cost-effectiveness of genetic testing to guide the selection or dose of medications?

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Presentation overview

- Background ✓
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Methods: PICO

- PICO
  - **P**opulation: People any age who are prescribed medications for the conditions of interest
  - **I**nterventions: Pharmacogenomic tests to inform the selection or dose of psychotropic medications relevant to the conditions of interest
  - **C**omparisons: Usual care/no genetic testing
  - **O**utcomes: Decision-making regarding drug choice/dose; patient adherence to treatment regimen; patient response to treatment, adverse events as a result of treatment; cost-effectiveness or cost

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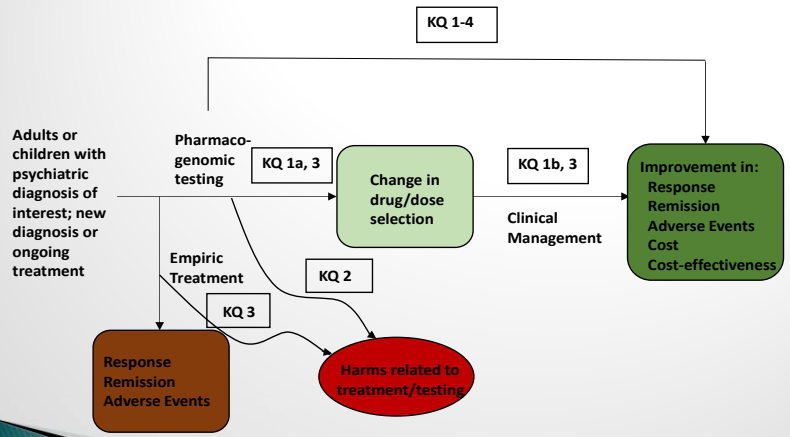
Methods: Analytic Framework

Figure 1. Analytic Framework: Pharmacogenetic Testing for Selected Conditions
(Key Questions referenced by number in the graphic)



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Methods: Literature Search

- Primary studies
  - PubMed: January 1, 2000 to November 28, 2016
  - Embase: 1996 to November 28, 2016
  - Exclusion criteria for all KQs
    - Non-English
    - Non-DNA-based laboratory tests
    - Studies without control groups

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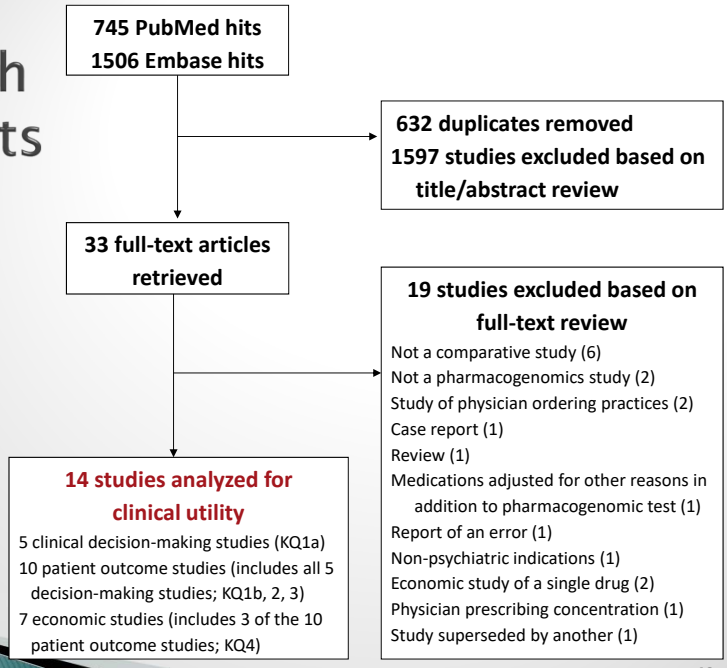
Search Results



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Quality Assessment Aligns with GRADE System (Appendix III)

- Individual **study** appraisal
  - *Are the findings **valid**?*
    - Study design, execution, and analysis (checklist)
    - Internal validity (minimization of bias)
    - *Good–Fair–Poor–Very Poor*
- Evaluation of **body of evidence** for each outcome
  - *How **confident** are we that this evidence answers the Key Question?*
    - Domains:
      - –Study design and weaknesses
      - –Quantity/precision of data
      - –Publication bias
      - –Applicability to PICOS
      - –Consistency, study findings
    - *High–Moderate–Low–Very Low*

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Presentation overview

- Background ✓
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Findings: Decision-making (KQ1a)

Number, Size, and Quality of Studies	Key Study Results
4 studies Exp n=183 Ctl n=183 ***Depressive disorders*** Singh 2015 RCT, fair Funding: Not reported Winner 2013 RCT, fair Funding: Assurex Hall-Flavin 2012 Controlled trial, fair Funding: Assurex Breitenstein 2014 Comparative, poor Funding: Non-commercial	**Singh 2015** (Exp n=74) CNSDose • Treatment prescribers indicated that in 65% of cases, a PGx panel interpretive report led to medication dosing different from their usual practice. GeneSight **Winner 2013** (Exp n=26 vs Ctl n=25; all genotyped) • 100% of baseline medications that a PGx panel interpretive report indicated should be used with caution and frequent monitoring were changed in the Exp group; 50% of similarly classified medications were changed/dose adjusted in Ctls. **Hall-Flavin 2012** (Exp n=25 vs Ctl n=26; all genotyped) • At 8 weeks, 5.9% of Exp cases were prescribed a medication designated "use with caution" on PGx panel interpretive report vs 21.4% of controls (*P*=0.02). GeneSight **Breitenstein 2014** (Exp n=58) • By 5 weeks, prescribers increased dose of appropriate antidepressants 1.63-fold for genotyped pts (Exp) with an unfavorable *ABCB1* genotype (*P*=0.012) and changed antidepressant prescribed more often (*P*=0.011) compared with other genotypes.

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Findings: Decision-making (KQ1a)

Number, Size, and Quality of Studies	Quality of Evidence	Direction of Findings
4 studies Exp n=183 Ctl n=183 ***Depressive disorders*** Singh 2015 RCT, fair Winner 2013 RCT, fair Hall-Flavin 2012 Controlled trial, fair Breitenstein 2014 Comparative, poor	**OVERALL: LOW** Study quality: Poor-Fair Quantity and precision: Few studies, small sample sizes, some pt populations limited by race/ethnicity; precision unknown Consistency: Outcomes generally consistent; not measured similarly Applicability to PICO: ✓ Reference standard: ✓ Publication bias: Unknown	Limited results suggest that PGx test results, whether single-gene or interpretive panels, may change prescribing patterns in favor of PGx recommendations compared with treatment as usual.

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Findings: Rating Scales for Depression

Instrument	Number of Items	Score Range	Interpretation
Hamilton Depression Rating Scale (HAM-D)	17	0-50	≤7 not depressed ≥14 at least moderately depressed
Quick Inventory of Depressive Symptomatology (QIDS), clinician rating or self report	16	1-27	≤5 not depressed ≥11 at least moderately depressed
Patient Health Questionnaire-9 (PHQ-9)	9	1-27	≤4 minimal depression ≥10 at least moderately depressed

STAR*D Study: Develop and evaluate feasible treatment strategies to improve clinical outcomes for real-world patients with treatment-resistant depression.

- Primary outcome (remission): HAM-D17 ≤7 (≥14 at baseline)
- Secondary outcome (response): Reduction in the QIDS-SR16 score of ≥50%

≥50% ↓ PHQ-9 is a National Quality Measures Clearinghouse clinical quality measure

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Findings: Impact on Patient Outcomes (KQ1b)

Number, Size, and Quality of Studies	Key Study Results (statistically significant results bolded)
KQ #1b. Outcome: Remission	
4 studies Exp n=272 Ctl n=270 ***Depressive disorders*** Winner 2013 RCT, fair Funding: Assurex Singh 2015 RCT, fair Funding: Not reported Hall-Flavin 2013 Controlled trial, fair Funding: Assurex Breitenstein 2014 Comparative, poor Funding: non-commercial	**Winner 2013** (Exp n=26 vs Ctl n=25) • At 10 weeks, 20% of Exp pts vs 8.3% of Ctl pts achieved remission (HAM-D17 <7) (**OR=2.75**; 95% CI, 0.48-15.8; *P*=NS). **Singh 2015** (Exp n=74 vs Ctl n=74) • At 12 weeks, Exp pts more often obtained remission (HAM-D17 <7) (**OR=2.52**; 95% CI, 1.71-3.73; *P*<0.0001). • Number needed to test for remission=3 (95% CI, 1.7-3.5). **Hall-Flavin 2013** (Exp n=114 vs Ctl n=113) • At 8 weeks, more Exp pts obtained remission (QIDS-C16 <6) compared with Ctl pts (**OR=2.42**; 95% CI, 1.09-5.39; *P*=0.03). • HAM-D17 and PHQ-9 results were not significantly different except for results using data imputation to account for 27% lost to follow-up. **Breitenstein 2014** (Exp n=58 vs Ctl n=58) • Exp pts more often in remission (HAM-D21 <10) at treatment week 4 compared with Ctl pts (**83.6% vs 62.1%**; *P*=0.005). HAM-D21 at admission ≥14. Required change in score may not be clinically relevant.

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Findings: Impact on Patient Outcomes (KQ1b)

Number, Size, and Quality of Studies	Quality of Evidence	Direction of Findings
KQ #1b. Outcome: Remission		
4 studies Exp n=272 Ctl n=270 ***Depressive disorders*** Winner 2013 RCT, fair Singh 2015 RCT, fair Hall-Flavin 2013 Controlled trial, fair Breitenstein 2014 Comparative, poor	**OVERALL: LOW** Study quality: Poor-Fair Quantity and precision: Few studies, small sample sizes, studies do not address all indications of interest, some pt populations limited by race/ethnicity; precision unknown Consistency: Remission outcomes range from highly statistically significant to not significant, may be related to study size; not all measured similarly Applicability to PICO: ✓ Reference standard: ✓ Publication bias: Unknown	In all studies, the direction of results suggests that genotyped pts are more likely to obtain remission. But results are not consistently statistically significant and in 1 study may not be clinically relevant.

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Findings: Impact on Patient Outcomes (KQ1b)

Number, Size, and Quality of Studies	Key Study Results
KQ #1b. Outcome: Response to treatment	
6 studies Exp n=365 Ctl n=413 ***Depressive disorders*** Winner 2013 RCT, fair Funding: Assurex Hall-Flavin 2013 Controlled trial, fair Funding: Assurex Hall-Flavin 2012 Controlled trial, fair Funding: Assurex Rundell 2011 Comparative, very poor Funding: Assurex	**Winner 2013** (Exp n=26 vs Ctl n=25, all genotyped) • At 10 weeks, 36% of Exp pts responded (>50% reduction in HAM-D17) vs 20.8% of Ctl pts (**OR=2.14**; 95% CI, 0.59-7.69; *P*=NS). **Hall-Flavin 2013** (Exp n=114 vs Ctl n=113, all genotyped) • At 8 weeks, more Exp pts responded (>50% reduction in score from baseline) vs Ctl pts as measured by: – QIDS-C16 (**OR=2.58**; 95% CI, 1.33-5.03; *P*=0.005), – HAM-D17 (**OR=2.06**; 95% CI, 1.07-3.95; *P*=0.03), and – PHQ-9 (**OR=2.27**; 95% CI, 1.20-4.30; *P*=0.01). – Results using data imputation to account for 27% loss to follow-up were statistically significant except for QIDS-C16. **Hall-Flavin 2012** (Exp n=25 vs Ctl n=26; all genotyped) • 8-week score reductions: – QIDS-C16: **31.2%** for Exp pts vs **7.2%** for controls (*P*=0.002) – HAM-D17: **30.8%** for Exp pts vs **18.2%** for controls (*P*=0.04) **Rundell 2011** (Exp n=29 vs Ctl n=17) • *CYP450* categories: No significant differences in serial PHQ-9 scores. • *5-HTTLPR* categories: L/L genotype pts had greater PHQ-9 score improvement than other genotypes at times 4 and 5 (*P*=0.02 to *P*=0.05). • Adjusted post-day 14 PHQ-9 scale slopes and differences in pre- to post-baseline scale slopes were not significantly different among genotypes.

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Findings: Impact on Patient Outcomes (KQ1b)

Number, Size, and Quality of Studies	Key Study Results
KQ #1b. Outcome: Response to treatment	
6 studies Exp n=365 Ctl n=413 ***Any psychiatric diagnosis*** Espadaler 2016 Comparative, poor Funding: AB-Biotics? ***Alcohol use*** Oslin 2015 Observational within RCT, poor Funding: NIAAA; VA	**Espadaler 2016** (Exp n=89 vs Ctl n=93) • At 3 months, 93% (Exp) vs 82% (Ctl) had CGI-S scores lower than baseline (adjusted **OR=3.86**; 95% CI, 1.36-10.95; *P*=0.011). **Oslin 2015** (Exp n=38 naltrexone + 44 placebo, all asp40) (Ctl n=73 naltrexone + 66 placebo, all asn40) • Exp (asp40, favorable genotype) pts: OR for heavy drinking in the naltrexone group was 1.10 (95% CI, 0.52-2.31; *P*=0.80) compared with placebo. • Ctl (asn40, unfavorable genotype) pts: OR for heavy drinking in the naltrexone group was 0.69 (95% CI, 0.41-1.18; *P*=0.17) compared with placebo.

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Findings: Impact on Patient Outcomes (KQ1b)

Number, Size, and Quality of Studies	Quality of Evidence	Direction of Findings
KQ #1b. Outcome: Response to treatment		
6 studies Exp n=365 Ctl n=413 ***Depressive disorders*** Winner 2013 (RCT, fair) Hall-Flavin 2013 (controlled trial, fair) Hall-Flavin 2012 (controlled trial, fair) Rundell 2011 (comparative, very poor) ***Any psychiatric diagnosis*** Espadaler 2016 (comparative, poor) ***Alcohol use*** Oslin 2015 (observational within RCT, fair)	OVERALL: LOW Study quality: Very poor - Fair Quantity and precision: Studies limited in quantity and size, studies do not address all indications of interest, some pt populations limited by race/ethnicity; precision unknown Consistency: Response outcomes range from highly statistically significant to not significant; not all measured similarly; studies may not define clinically significant response; better study designs tend to obtain statistically significant results, depending on size Applicability to PICO: ✓ Reference standard: ✓ Publication bias: Unknown	Results are in the direction of improved response for genotyped pts. Only 1 study used predefined measures of response and obtained statistically significant results. In the naltrexone trial for alcohol use, results were opposite those of prior studies, although not statistically significant.

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Findings: Impact on Patient Outcomes (KQ1b)

Outcome	Indications	Studies	Study Quality	Overall Quality
Adherence, tolerance, adverse events	Depressive disorders; any psychiatric diagnosis; alcohol use	3 studies Exp n=274 Ctl n=389 1 study Exp n=1662 Ctl n=10880	Poor-Fair	**VERY LOW**
Hospital stay, healthcare utilization	Depressive disorders	1 study Exp n=58 Ctl n=58	Poor	**VERY LOW**

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Findings: KQ2, KQ3

- Direct harms of pharmacogenetics testing (KQ2)
  - No studies found.
- Variation in decision-making, patient outcomes, or harms by patient subgroups or characteristics (KQ3)
  - 8 of 9 studies compared tested vs not tested study arm populations at baseline and found few statistically significant differences.
  - One poor-quality retrospective comparative study found, in a multivariate logistic regression model, that neither clinical history variables nor patient characteristic variables were statistically significant predictors of response to medication treatment (measured by a depression severity scale).

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Findings: Costs of Genetic Testing (KQ4)

Number and Type of Studies	Study Results
Cost-Comparison Studies	
4 studies Exp n=1921 Ctl n=11253 Winner 2015 (pharmacy benefits provider database; mixed psychiatric diagnoses) Funding: Assurex Fagerness 2014 (medical and pharmacy claims database; mixed psychiatric diagnoses) Funding: Genomind Herbild 2013 (Danish patient registers; schizophrenia) Funding: Danish Gov't Rundell 2011 (Mayo Clinic database; depression) Funding: Assurex	**Winner 2015**, GeneSight (n=1662) vs propensity-matched Ctl (n=10,880): • Meds congruent with PGx test results had net annual pharmacy cost savings of $2775 vs incongruent meds; *P*<0.0001 **Fagerness 2014**, Genecept (n=111) vs propensity-matched controls (n=222): • Measured costs of all medications and all outpatient medical visits 4 months prior to and after PGx test results available to clinician • Total costs increased by 5.9% (PGx) and 15.4% (Ctl) • Relative cost savings for PGx $562 (9.5%) per PGx pt vs Ctl **Herbild 2013**, *CYP2D6* and *CYP2C19* PGx test (n=103) vs controls (n=104) • Schizophrenia spectrum pts • Calculated total costs of treating each pt for 1 year, including primary and secondary care services, psychiatric hospital care, and medications • Mean total costs/year $18.4k PGx vs $21.6k Ctl, very wide CIs, both estimates affected by high outliers • Modeling suggests PGx testing significantly reduced costs for extreme metabolizers **Rundell 2011**, PGx testing (≤1 of *CYP2D6*, *CYP2C19*, *CYP2C9*, *5-HTTLPR*; n=45) vs standard care controls (n=47): • Total healthcare utilization costs for pt subset who lived in community during study and received all healthcare at Mayo Clinic Rochester; pre-baseline costs subtracted from post-baseline costs • Mean total costs $5010 PGx vs $6693 Ctl; *P*=0.08

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Findings: Costs of Genetic Testing (KQ4)

Number and Type of Studies	Study Results
Cost-Effectiveness Studies	
2 modeling studies Perlis 2009 (modeled from STAR*D) Funding: Non-commercial Olgiati 2012 (modeled from STAR*D) Funding: Not reported	**Perlis 2009**, *HTR2A* PGx testing vs none in pts with major depressive disorder • Direct medical costs, including outpatient and inpatient treatment, meds • Test 1st + bupropion tx for test-negative pts ↑ cost by $505/pt but provided 0.0054 QALY for ICER of $93,520/QALY; therefore, not cost-effective **Olgiati 2012**, *5-HTTLPR* PGx testing vs none for major depressive disorder • Estimated costs of medications, outpatient and inpatient care, and genetic testing in Western European healthcare systems • Estimated overall cost of healthcare Intl $2242 (PGx) vs Intl $2063 (Ctl) • Incremental cost of PGx testing was Intl. $179 and the ICER was Intl. $1147
Cost-Utility Studies	
1 study, n=323 Herbild 2009 (questionnaire) Funding: Non-commercial	**Herbild 2009** (n=323), willingness-to-pay for *CYP2D6* PGx: • Willingness to pay for a 10% probability of 1 antidepressant change or for the reduction of 1 month of time for dosage adjustments exceeded test cost in Denmark.

Summary: Results in some cases suggested cost-effectiveness but lacked consistency overall. There were indications that results may depend at least partly on test cost and on the effect size of the clinical validity evidence supporting the pharmacogenomic test. Modeling results are limited by assumptions, tests chosen, and quality of supporting data.

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Presentation overview

- Background ✓
- Objectives ✓
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- Overall Summary and Discussion

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Practice Guidelines

GL Quality	Pharmacogenomics Recommendations
Depressive Disorders	
Good: ICSI; beyondblue Fair: WFSBP; VA/DoD; Poor: EPA	**Four of 5 GLs present no formal recommendations for the use of PGx testing.** **WFSBP:** In possibly nonadherent pts (e.g., low drug plasma levels despite high doses of the antidepressant), a combination of TDM and genotyping may be informative. Such analyses can aid in identifying slow or rapid metabolizers of certain antidepressants.
Other	
Fair: CPIC × 2 Poor: AGNP; BAP	**Two CPIC GLs provide dosing recommendations for tricyclic antidepressants or SSRIs based on *CYP2D6* or *CYP2D6* gene phenotypes.** For *CYP2D6* or *CY2C19* ultrarapid metabolizers with increased metabolism of a medication, an alternative drug not predominantly metabolized by either the *CYP2D6* or *CY2C19* gene phenotype should be selected. For *CYP2D6* or *CY2C19* extensive or intermediate metabolizers, CPIC recommends initiating therapy with the recommended starting dose; *except* for *CYP2D6* intermediate metabolizers of tricyclic antidepressants, CPIC recommends a 25% reduction of the starting dose and TDM to guide dose adjustments. For *CYP2D6* or *CY2C19* poor metabolizers with greatly reduced metabolism of tricyclic antidepressants or SSRIs, CPIC recommends a 25% to 50% reduction of the recommended starting dose and TDM to guide dose adjustments.

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Payer Policies

- Aetna, Group Health Cooperative, and Regence Group:
  - Commercial pharmacogenomic gene panels such as **GeneSight** and **Genecept Assay** are considered experimental, investigational, and/or not medically necessary for managing psychiatric conditions.
  - There is insufficient evidence that these genetic testing panels result in improved patient health outcomes.
- No guidance from Oregon HERC
- No CMS National Coverage Determinations
- Noridian Healthcare Solutions LLC (Medicare contractor, WA)
  - Local Coverage Decision (October 1, 2015) for **GeneSight Psychotropic**: Provides limited coverage when licensed psychiatrists or neuropsychiatrists are contemplating an alteration in neuropsychiatric medication for patients diagnosed with major depressive disorder who are suffering with refractory moderate to severe depression after at least 1 prior neuropsychiatric medication failure.
  - Local Coverage Decision (July 8, 2016) for ***CYP2D6* genetic testing** is considered medically necessary to guide medical treatment and/or dosing for individuals for whom initial therapy is planned with amitriptyline or nortriptyline for treatment of depressive disorders.

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Presentation overview

- Background ✓
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Summing up . . .

- Key Points
  - LOTS of data!
    - Gene–outcome associations (clinical validity)
    - Low effect size, hypothesis-generating
    - Few data show how to combine gene results and categorize patients
    - Commercial panels use proprietary methods of synthesis
  - Clinical utility: Medical decision-making
    - Consistent but limited evidence indicates pharmacogenomic test results lead treatment prescribers to change their treatment decisions
    - Not sufficient to support a conclusion of clinical benefit
  - Clinical utility: Healthcare outcomes
    - Evidence is extremely limited and compromised
    - Low to very low quality, depending on the outcome measured
    - Clinical utility for PGx is not generalizable!

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Quality of the Body of Evidence

High
- Reliable evidence reflecting the true effect
- Unlikely to change with future studies

Moderate
- Reasonable confidence that the results represent the true direction of effect
- The effect estimate might change with future studies

Low
- Little confidence due to poor quality and/or mixed results and/or a paucity of studies
- **Future studies are likely to change the estimates and possibly the direction**

Very Low
- **No confidence in any result found (e.g., paucity of data)**
- Data are such that we cannot make a statement on the findings

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Summing up . . .

- Evidence base
  - Insufficient regarding the clinical effectiveness of pharmacogenomic testing to aid in the treatment of the psychiatric disorders of interest for this report

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Thank you!

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Extra Slides

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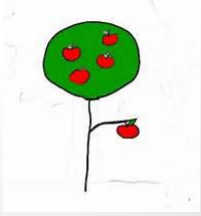
BACKGROUND – Clinical Validity

- Includes the strength of the association between gene variants and treatment outcomes
- May be reported as odds ratios (OR)
- OR can be converted to effect size or Cohen's d
- Suggested interpretation of Cohen's d:

OR	Cohen's d	Interpretation
2.3	0.2	Small
8.0	0.5	Medium
28.0	0.8	Large



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BACKGROUND – Clinical Validity

- We collected systematic reviews and meta-analyses of pharmacogenomic gene-outcome associations for the indications of interest.
- Using schizophrenia as an example, we synthesized representative meta-analyses for 15 genes and a variety of outcomes.
- ORs are no higher than 4.3 (d=0.35) and mostly <2 (d<0.17).
- No meta-analyses combined results for more than one gene for the same outcome to show improved effect size.
- Study designs may not correct for multiple potential confounders.

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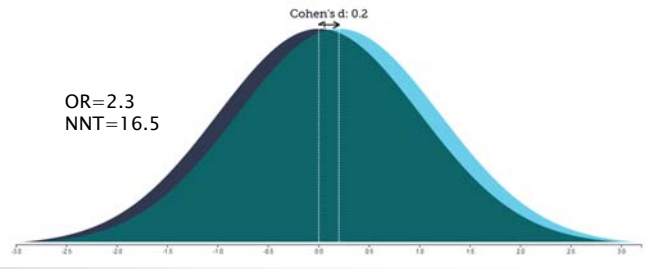
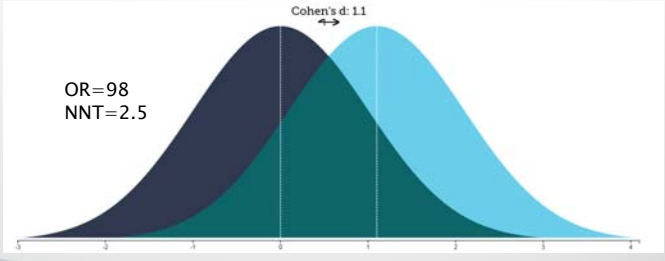
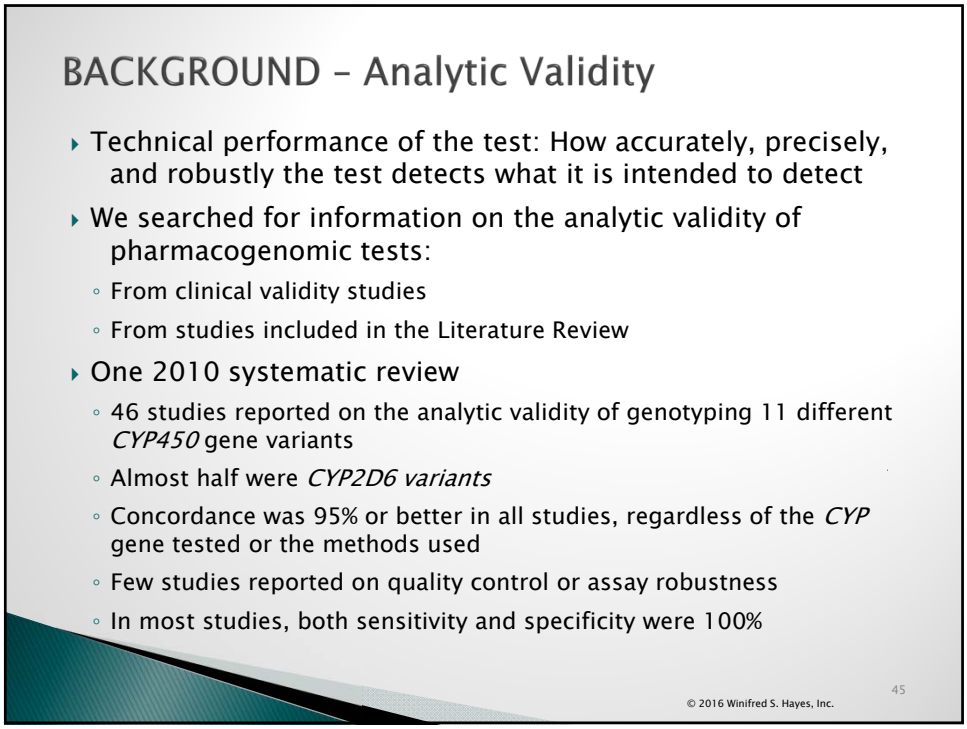
BACKGROUND – Clinical Validity



Interpreting Cohen's d effect size: an interactive visualization created by Kristoffer Magnusson
http://rpsychologist.com/d3/cohend/



44


BACKGROUND – Analytic Validity
Technical performance of the test: How accurately, precisely, and robustly the test detects what it is intended to detect
We searched for information on the analytic validity of pharmacogenomic tests:
From clinical validity studies
From studies included in the Literature Review
One 2010 systematic review
46 studies reported on the analytic validity of genotyping 11 different CYP450 gene variants
Almost half were CYP2D6 variants
Concordance was 95% or better in all studies, regardless of the CYP gene tested or the methods used
Few studies reported on quality control or assay robustness
In most studies, both sensitivity and specificity were 100%
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Washington State Health Care Authority

Final key questions and background

Pharmacogenetic testing for selected conditions

Background

In 2014, there were an estimated 43.6 million (18.1 percent) adults in the United States with a mental illness in the previous year. This includes approximately 9.8 million (4.2 percent) adults with serious mental illness. Based on data from 2002, the National Institute of Mental Health (NIMH) estimates that the total direct and indirect costs of serious mental illness exceeds $300 billion per year. In 2010, neuropsychiatric disorders, which include mental and behavioral disorders, accounted for the largest proportion of health-related disability in the U.S. In 2008, 13.4 percent of adults in the United States received treatment for a mental health problem. This includes all adults who received care in inpatient or outpatient settings and/or used prescription medication for mental or emotional problems. The following mental illnesses are the focus of this report: depression, psychosis, anxiety, mood disorders, attention deficit hyperactivity disorder (ADHD), and substance use disorder. Substance abuse will focus specifically on opioid and alcohol abuse.

Depression, psychosis, mood disorders, and anxiety are treated by various medications, including tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), typical antipsychotics, and atypical antipsychotics. However, there is a 30 percent to 50 percent failure rate with initial treatment, and rates of attrition and nonadherence during treatment are reported to be high. While some patients experience benefits from these medications, response varies significantly among patients and can range from no response at all to medication-related toxicity and serious side effects after a standard dose. The reason for such variability is not fully understood, although it is believed that both genetics and environment play a role.

Attention deficit hyperactivity disorder (ADHD), a neurodevelopmental disorder, can affect young children, adolescents, and adults. Symptoms vary from mild to severe. Data from 2011 indicate that 6.4 million (11%) children ages 4 to 17 years in the U.S. had been diagnosed with ADHD at some point in their lives, and 3.5 million (6%) 4 to 17 year olds were taking medication for ADHD. Approximately 4.1 percent of adults in the U.S. in 2005 reported having ADHD in the previous year, and 41.3 percent of this group are considered to have “severe disorder.” Medications such as stimulants and non-stimulants may be prescribed for the treatment of ADHD.

Substance use disorder affects approximately 20 million adults in the U.S. and is a frequent cause of illness, injury or death and subsequently places a significant burden on the health care system and individuals and families. It includes misuse or dependence on drugs and alcohol. Medication-assisted treatment may be used to reduce cravings or symptoms of withdrawal from opioids or alcohol. The medications generally act to either reduce or eliminate sensations associated with using a substance or cause a negative reaction when a substance is taken.

Pharmacogenomics aims to identify relationships between variations in genes that affect medication response and clinical outcomes and ultimately identify patients likely to respond to treatment or experience adverse events from specific medications. Numerous enzymes and other types of effector molecules are known to be involved with drug uptake, distribution, metabolism, target engagement, and action. Specific variants in the genes encoding these molecules may result in an absence of function, reduced activity, or increased activity, thereby affecting drug function. The labels of several medications include a discussion of pharmacogenetics or drug interactions for some genes; far fewer include recommendations for how to use this information in patient management. Many tests for these variants are commercially available in the U.S. Targeted tests of individual genes and multi-gene panels designed to test several selected genes at once are available to identify specific variants in each gene that are believed to be associated with drug response or potential adverse reactions. Available panels have some overlap in the genes included in each panel, but not all panels test the same genes. Those that do may not assess the same variants for a given gene. Potential uses for the information gleaned from both types of tests include drug and dose selection for initiating or changing medications with the intent to improve patient outcomes and experiences with treatment.

Policy Context

A growing number of new laboratory tests and computer based predictive algorithms are available to assess an individual patient's potential metabolic response to various drugs. Potential benefits include better application of the drugs for a specific individual. Concerns relate to whether specific tests result in improved treatment decisions and health outcomes, as well as rapid emergence and uptake of pharmacogenetics tests generally. Concerns are considered low for safety of these tests, high for efficacy, and medium/high for cost-effectiveness.

Scope

Population: Adults and children initiating or changing medications for any of the following diagnoses: depression, mood disorder, psychosis, anxiety, attention deficit hyperactivity disorder (ADHD), and substance use disorder (specifically opioid and alcohol abuse)

Interventions: Genetic tests to inform the selection or dose of medications for specified disorders

Comparators: Usual care/no genetic testing

Outcomes:

- Effect of genetic testing on patient management decisions about medication selection or dose
- Effect of genetic testing on patient adherence to treatment regimen
- Effect of patient management decisions guided by genetic testing on response to treatment and adverse events as a result of treatment
- Direct harms of genetic testing such as consequences of false positives or negatives, and risks associated with sample collection
- Costs and cost-effectiveness

Settings: Inpatient or outpatient settings, any country.

Key Questions

1. Effectiveness: What is the clinical utility of genetic testing to inform the selection or dose of medications for individuals diagnosed with depression, mood disorders, psychosis, anxiety, attention deficit hyperactivity disorder (ADHD), or substance use disorder?
    a. Does genetic testing to inform the selection or dose of medications change the drug or dose selected by physicians and/or patients compared with usual care/no genetic testing?
    b. Do decisions about selection or dose of medications guided by genetic testing result in clinically meaningful improvement in patient response to treatment, or reduction in adverse events as a result of treatment compared with decisions based on usual care/no genetic testing?
2. Harms: What direct harms are associated with conducting genetic testing when it is used to inform the selection or dose of medications?
3. Special populations: Compared with usual care/no genetic testing, do decisionmaking, patient outcomes, or harms following genetic testing to inform the selection or dose of medications vary by:
    a. Clinical history (e.g. prior treatments, whether the diagnosis is initial or recurrent, duration of diagnosis, severity of illness, or concurrent medications); or
    b. Patient characteristics (e.g. such as age, sex, or co-morbidities)?
4. Costs: What are the costs and cost-effectiveness of genetic testing to guide the selection or dose of medications?

Public Comment & Response

No comments were received regarding the draft key questions.

HTCC Coverage and Reimbursement Determination Analytic Tool

HTA's goal is to achieve *better health care outcomes* for enrollees and beneficiaries of state programs by paying for proven health *technologies that work*.

To find best outcomes and value for the state and the patient, the HTA program focuses on three questions:

1. Is it safe?
2. Is it effective?
3. Does it provide value (improve health outcome)?

The principles HTCC uses to review evidence and make determinations are:

Principle One: Determinations are evidence-based

HTCC requires scientific evidence that a health technology is safe, effective and cost-effective[1] as expressed by the following standards[2]:

- Persons will experience better health outcomes than if the health technology was not covered and that the benefits outweigh the harms.
- The HTCC emphasizes evidence that directly links the technology with health outcomes. Indirect evidence may be sufficient if it supports the principal links in the analytic framework.
- Although the HTCC acknowledges that subjective judgments do enter into the evaluation of evidence and the weighing of benefits and harms, its recommendations are not based largely on opinion.
- The HTCC is explicit about the scientific evidence relied upon for its determinations.

Principle Two: Determinations result in health benefit

The outcomes critical to HTCC in making coverage and reimbursement determinations are health benefits and harms[3]:

- In considering potential benefits, the HTCC focuses on absolute reductions in the risk of outcomes that people can feel or care about.
- In considering potential harms, the HTCC examines harms of all types, including physical, psychological, and non-medical harms that may occur sooner or later as a result of the use of the technology.
- Where possible, the HTCC considers the feasibility of future widespread implementation of the technology in making recommendations.
- The HTCC generally takes a population perspective in weighing the magnitude of benefits against the magnitude of harms. In some situations, it may make a determination for a technology with a large potential benefit for a small proportion of the population.
- In assessing net benefits, the HTCC subjectively estimates the indicated population's value for each benefit and harm. When the HTCC judges that the balance of benefits and harms is likely to vary substantially within the population, coverage or reimbursement determinations may be more selective based on the variation.

[1] Based on Legislative mandate: See RCW 70.14.100(2).

[2] The principles and standards are based on USPSTF Principles at: http://www.ahrq.gov/clinic/ajpmsuppl/harris3.htm

[3] The principles and standards are based on USPSTF Principles at: http://www.ahrq.gov/clinic/ajpmsuppl/harris3.htm

- The HTCC considers the economic costs of the health technology in making determinations, but costs are the lowest priority.

Using evidence as the basis for a coverage decision

Arrive at the coverage decision by identifying for Safety, Effectiveness, and Cost whether (1) evidence is available, (2) the confidence in the evidence, and (3) applicability to decision.

1. Availability of Evidence:

Committee members identify the factors, often referred to as outcomes of interest, that are at issue around safety, effectiveness, and cost. Those deemed key factors are ones that impact the question of whether the particular technology improves health outcomes. Committee members then identify whether and what evidence is available related to each of the key factors.

2. Sufficiency of the Evidence:

Committee members discuss and assess the evidence available and its relevance to the key factors by discussion of the type, quality, and relevance of the evidence[4] using characteristics such as:

- Type of evidence as reported in the technology assessment or other evidence presented to committee (randomized trials, observational studies, case series, expert opinion);
- The amount of evidence (sparse to many number of evidence or events or individuals studied);
- Consistency of evidence (results vary or largely similar);
- Recency (timeliness of information);
- Directness of evidence (link between technology and outcome);
- Relevance of evidence (applicability to agency program and clients);
- Bias (likelihood of conflict of interest or lack of safeguards).

Sufficiency or insufficiency of the evidence is a judgment of each clinical committee member and correlates closely to the GRADE confidence decision.

Not Confident	Confident
Appreciable uncertainty exists. Further information is needed or further information is likely to change confidence.	Very certain of evidentiary support. Further information is unlikely to change confidence

3. Factors for Consideration - Importance

At the end of discussion a vote is taken on whether sufficient evidence exists regarding the technology's safety, effectiveness, and cost. The committee must weigh the degree of importance that each particular key factor and the evidence that supports it has to the policy and coverage decision. Valuing the level of importance is factor or outcome specific but most often include, for areas of safety, effectiveness, and cost:

[4] Based on GRADE recommendation: http://www.gradeworkinggroup.org/FAQ/index.htm

- Risk of event occurring;
- The degree of harm associated with risk;
- The number of risks; the burden of the condition;
- Burden untreated or treated with alternatives;
- The importance of the outcome (e.g. treatment prevents death vs. relief of symptom);
- The degree of effect (e.g. relief of all, none, or some symptom, duration, etc.);
- Value variation based on patient preference.

Clinical Committee Findings and Decisions

Efficacy Considerations

- What is the evidence that use of the technology results in more beneficial, important health outcomes? Consider:
  - Direct outcome or surrogate measure
  - Short term or long term effect
  - Magnitude of effect
  - Impact on pain, functional restoration, quality of life
  - Disease management
- What is the evidence confirming that use of the technology results in a more beneficial outcome, compared to no treatment or placebo treatment?
- What is the evidence confirming that use of the technology results in a more beneficial outcome, compared to alternative treatment?
- What is the evidence of the magnitude of the benefit or the incremental value?
- Does the scientific evidence confirm that use of the technology can effectively replace other technologies or is this additive?
- For diagnostic tests, what is the evidence of a diagnostic tests' accuracy?
  - Does the use of the technology more accurately identify both those with the condition being evaluated and those without the condition being evaluated?
- Does the use of the technology result in better sensitivity and better specificity?
- Is there a tradeoff in sensitivity and specificity that on balance the diagnostic technology is thought to be more accurate than current diagnostic testing?
- Does use of the test change treatment choices?

Safety

- What is the evidence of the effect of using the technology on significant morbidity?
  - Frequent adverse effect on health, but unlikely to result in lasting harm or be life-threatening, or;
  - Adverse effect on health that can result in lasting harm or can be life-threatening?
- Other morbidity concerns?
- Short term or direct complication versus long term complications?
- What is the evidence of using the technology on mortality – does it result in fewer adverse non-fatal outcomes?

Cost Impact

- Do the cost analyses show that use of the new technology will result in costs that are greater, equivalent or lower than management without use of the technology?

Overall

- What is the evidence about alternatives and comparisons to the alternatives?
- Does scientific evidence confirm that use of the technology results in better health outcomes than management without use of the technology?

Next Step: Cover or No Cover

If not covered, or covered unconditionally, the Chair will instruct staff to write a proposed findings and decision document for review and final adoption at the following meeting.

Next Step: Cover with Conditions

If covered with conditions, the Committee will continue discussion.

1) Does the committee have enough information to identify conditions or criteria?
    - Refer to evidence identification document and discussion.
    - Chair will facilitate discussion, and if enough members agree, conditions and/or criteria will be identified and listed.
    - Chair will instruct staff to write a proposed findings and decision document for review and final adoption at next meeting.

2) If not enough or appropriate information, then Chair will facilitate a discussion on the following:
    - What are the known conditions/criteria and evidence state
    - What issues need to be addressed and evidence state

The chair will delegate investigation and return to group based on information and issues identified. Information known but not available or assembled can be gathered by staff ; additional clinical questions may need further research by evidence center or may need ad hoc advisory group; information on agency utilization, similar coverage decisions may need agency or other health plan input; information on current practice in community or beneficiary preference may need further public input. Delegation should include specific instructions on the task, assignment or issue; include a time frame; provide direction on membership or input if a group is to be convened.

Clinical Committee Evidence Votes

First Voting Question

The HTCC has reviewed and considered the technology assessment and information provided by the administrator, reports and/or testimony from an advisory group, and submissions or comments from the public. The committee has given greatest weight to the evidence it determined, based on objective factors, to be the most valid and reliable.

HEALTH TECHNOLOGY EVIDENCE IDENTIFICATION

Discussion Document: What are the key factors and health outcomes and what evidence is there? (Applies to the population in the PICO for this review)

Safety Outcomes	Importance of Outcome	Safety Evidence / Confidence in Evidence
Adverse events		

Efficacy – Effectiveness Outcomes	Importance of Outcome	Efficacy / Effectiveness Evidence
Treatment decision-making		
Drug dosing		
Treatment Adherence		
Response to treatment		
Treatment Tolerance		

Cost Outcomes	Importance of Outcome	Cost Evidence
Cost-utility		
Cost-effectiveness		
Direct cost		

Special Population / Considerations Outcomes	Importance of Outcome	Special Populations/ Considerations Evidence
Clinical history		
Patient characteristics		

HEALTH TECHNOLOGY EVIDENCE IDENTIFICATION

For Safety: Is there sufficient evidence that the technology is safe for the indications considered?

Unproven (no)	Less (yes)	Equivalent (yes)	More in some (yes)	More in all

For Efficacy/Effectiveness: Is there sufficient evidence that the technology has a meaningful impact on patients and patient care?

Unproven (no)	Less (yes)	Equivalent (yes)	More in some (yes)	More in all

For Cost Outcomes/Cost-Effectiveness: Is there sufficient evidence that the technology is cost-effective for the indications considered?

Unproven (no)	Less (yes)	Equivalent (yes)	More in some (yes)	More in all

Discussion

Based on the evidence vote, the committee may be ready to take a vote on coverage or further discussion may be warranted to understand the differences of opinions or to discuss the implications of the vote on a final coverage decision.

- Evidence is insufficient to make a conclusion about whether the health technology is safe, efficacious, and cost-effective;
- Evidence is sufficient to conclude that the health technology is unsafe, ineffectual, or not cost-effective
- Evidence is sufficient to conclude that the health technology is safe, efficacious, and cost-effective for all indicated conditions;
- Evidence is sufficient to conclude that the health technology is safe, efficacious, and cost-effective for some conditions or in some situations

A straw vote may be taken to determine whether, and in what area, further discussion is necessary.

Second Vote

Based on the evidence about the technologies' safety, efficacy, and cost-effectiveness, it is

_____Not Covered _____ Covered Unconditionally _____ Covered Under Certain Conditions

Discussion Item

Is the determination consistent with identified Medicare decisions and expert guidelines, and if not, what evidence is relied upon.

Next Step: Proposed Findings and Decision and Public Comment

At the next public meeting the committee will review the proposed findings and decision and consider any public comments as appropriate prior to a vote for final adoption of the determination.

1) Based on public comment was evidence overlooked in the process that should be considered?

2) Does the proposed findings and decision document clearly convey the intended coverage determination based on review and consideration of the evidence?

Next Step: Final Determination

Following review of the proposed findings and decision document and public comments:

Final Vote

Does the committee approve the Findings and Decisions document with any changes noted in discussion?

If yes, the process is concluded.

If no, or an unclear (i.e., tie) outcome Chair will lead discussion to determine next steps.

Medicare Coverage and Guidelines

[From page 61 of the Final Evidence Report]

No CMS NCD for pharmacogenetics or pharmacogenomic testing was identified on September 23, 2016 at: CMS Advanced Search Database.

Guidelines

[From page 96-103 of the Final Evidence Report]

APPENDIX VIa. Detailed Summary of Practice Guidelines that Mention Pharmacogenomic Testing

Key: AGNP, Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie, APA, American Psychiatric Association; BAP, British Association for Psychopharmacology; CPIC, Clinical Pharmacogenetics Implementation Consortium; CV, clinical validity; DoD, Department of Defense; ECT, electroconvulsive therapy; EPA, European Psychiatric Association; ICSI, Institute for Clinical Systems Improvement; NR, not reported; PGx, pharmacogenomics; TDM, therapeutic drug monitoring; VA, Department of Veterans Affairs; WFSBP, World Federation of Societies for Biological Psychiatry

Sponsor, Year	Guideline Title	Relevant Recommendations		Quality/Main Limitations
		Pharmacogenomic Testing	Repeat Testing	
Depressive Disorders				
beyondblue (2010)	*Clinical practice guidelines: Depression in adolescents and young adults*	No formal recommendations for use of PGx testing. Guidelines state that PGx testing may specify treatment effectiveness in individuals with varying genotypes.	No recommendations	6.9 – Good (specific search terms and search strategy not reported)
EPA (Möller et al., 2011)	*Position statement of the European Psychiatric Association on the value of antidepressants in the treatment of unipolar depression*	No formal recommendations for use of PGx testing. Authors state that PGx testing is gaining increasing attention for the prediction of response to antidepressants in terms of individual pharmacokinetic and pharmacodynamics particularities; however further research is required to determine the respective significance of PGx testing. In addition, PGx testing may be specifically beneficial for the treatment of poor responders by making use of different treatment strategies (e.g., specific antidepressants, higher dosage, combination therapy, ECT, etc.) from the very beginning of treatment.	No recommendations	3.1 – Poor (systematic search methods and criteria for selecting evidence not described, methods for formulating consensus recommendations not described; guideline not reviewed by external experts; procedure for update of guideline NR)
ICSI (Trangle et al., 2016)	*Adult Depression in Primary Care*	No formal recommendations for use of PGx testing. The guideline states that cytochrome P450 testing can be used to determine genetic differences in the metabolism of particular medications, including antidepressants, and may help identify patients that are more sensitive to serious adverse reactions or medications with narrow therapeutic windows; however, the clinical significance and applicability of PGx testing to daily clinical practice has not yet been established.	No recommendations	6.7 – Good (methods for evaluation of bias and interpretation not described)
VA/DoD (2016)	*VA/DoD Clinical Practice Guideline for the Management of Major Depressive Disorder*	No formal recommendations for use of PGx testing.	No recommendations	5.9 – Fair

Sponsor, Year	Guideline Title	Relevant Recommendations		Quality/Main Limitations
		Pharmacogenomic Testing	Repeat Testing	
		The guideline states a need for a better understanding of the value and use of measurement-based care, including the place of PGx testing in the treatment of major depressive disorder. Currently there is insufficient evidence to support the routine use of genetic testing for the selection of antidepressant medication and further research is required in the use of genetic testing to aid in the selection of the most appropriate medication for a specific patient.		(guideline update process not described; source of funding NR)
WFSBP (Bauer et al., 2013)	*World Federation of Societies for Biological Treatment of Unipolar Depressive Disorders, Part 1: Update 2013 on acute and continuation treatment of unipolar depressive disorders*	Clinical Consensus Recommendation: In possibly non-adherent patients (e.g., low drug plasma levels despite high doses of the antidepressant), a combination of TDM and genotyping may be informative. Such analyses can aid in identifying those individuals who are slow or rapid metabolizers of certain antidepressants.	No recommendations	5.0 – Fair (search terms and dates literature covered NR; criteria for selecting evidence and how the body of evidence was evaluated for bias not described)
Schizophrenia Spectrum Disorders				
No guidelines addressing PGx testing specific to schizophrenia spectrum disorders were identified.				
Bipolar Disorder and Related Disorders				
No guidelines addressing PGx testing specific to bipolar disorder and related disorders were identified.				
Anxiety Disorders				
APA (Stein et al., 2009)	*Practice Guideline for the Treatment of Patients with Panic Disorder*	No formal recommendations for use of PGx testing. The guideline states that as our understanding of how genetic polymorphisms (e.g., cytochrome P450 isoenzymes) influence a patient's biological response to a medication (e.g., metabolism, sensitivity to side effects, etc.) expands, it will aid in the selection of individualized treatment.	No recommendations	5.7 – Fair (methods for evaluation of bias not described; procedure for update of guideline NR; pharmaceutical companies funded consensus meeting)
Attention Deficit/Hyperactivity Disorder				
No guidelines addressing PGx testing specific to attention deficit/hyperactivity disorder were identified.				
Substance Use Disorders				
APA (Kleber et al., 2006)	*Practice Guideline for the Treatment of Patients with Substance Use Disorders Second Edition*	No formal recommendations for use of PGx testing. The guideline states that cessation of substance use may be associated with changes in metabolism of medication (e.g., altered antipsychotic metabolism via cytochrome	No recommendations	5.3 – Fair (methods for formulating consensus recommendations and

Sponsor, Year	Guideline Title	Relevant Recommendations		Quality/Main Limitations
		Pharmacogenomic Testing	Repeat Testing	
		P450 1A2 with smoking cessation). Further research on the PGx approach to optimizing the choice of pharmacotherapy based on the gene or genes involved in the etiology or treatment responsiveness of substance use disorders may help guide identification of patient populations that will benefit from specific therapeutic options.		evaluation of bias not described)
BAP (Lingford-Hughes et al., 2012)	*BAP updated guidelines: evidence-based guidelines for the pharmacological management of substance abuse, harmful use, addiction and comorbidity: recommendations from BAP*	No formal recommendations for use of PGx testing. Guidelines state that a functional polymorphism, Asp40 allele, of the mu opioid receptor gene has been shown to predict naltrexone treatment response in alcohol-dependent individuals; however, this association may be moderated by other efficacious treatment or patient variables (e.g., motivation) (Evidence category Ib: Evidence from at least 1 RCT).	No recommendations	2.9 – Poor (systematic review not conducted; criteria for selecting evidence and how the body of evidence was evaluated for bias not described; guideline review and update process not described; competing interests of group members not declared)
Other				
AGNP (Baumann et al., 2005)	*The AGNP-TDM Expert Group Consensus Guidelines: focus on therapeutic monitoring of antidepressants*	No formal recommendations for use of PGx testing. Guidelines state that PGx testing alone has limited value, as environmental factors also regulate drug metabolism; however, PGx testing in combination with TDM may be beneficial and indicated in the following circumstances: • Metabolism of a medication is governed to a significant extent by the enzyme which is considered to be phenotyped or genotyped. • A medication's metabolism shows a wide interindividual variability as demonstrated by TDM. • A drug is characterized by a low therapeutic index. • The patient presents unusual plasma concentrations of the drug or its metabolites, and genetic factors are suspected to be responsible. • The patient suffers from a chronic illness that requires life-long treatment.	No recommendations	2.0 – Poor (systematic search methods and criteria for selecting evidence not described; methods for formulating recommendations not described; guideline not reviewed by external experts; guideline review and update process not described; competing interests of group members not declared; source of funding NR)
BAP (Cooper et al., 2016)	*BAP guidelines on the management of weight gain, metabolic disturbances and cardiovascular risk associated*	No formal recommendations for use of PGx testing. Guidelines state that genetic factors associated with drug-induced weight gain and its metabolic consequences	No recommendations	3.3 – Poor (systematic review not conducted; criteria for selecting evidence and how

Sponsor, Year	Guideline Title	Relevant Recommendations		Quality/Main Limitations
		Pharmacogenomic Testing	Repeat Testing	
	with psychosis and antipsychotic drug treatment	provide clues about the underlying mechanisms, and in the future may provide opportunities for personalized medicine in the predictive assessment of metabolic risk with antipsychotic drug treatment.		the body of evidence was evaluated for bias not described; guideline not reviewed by external experts; guideline review and update process not described; competing interests of grp members not declared)
CPIC (Hicks et al., 2013)	*Clinical Pharmacogenetics Implementation Consortium Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Tricyclic Antidepressants*	Dosing recommendations for amitriptyline and nortriptyline based on *CYP2D6* phenotype: *CYP2D6* ultrarapid metabolizer: • For increased metabolism of tricyclics to less active compounds as comparted with extensive metabolizers, avoid tricyclic use due to potential lack of efficacy. Consider alternative drug not metabolized by *CYP2D6*. (Strong) • If tricyclic is warranted, consider increasing the starting dose. Use therapeutic drug monitoring to guide dose adjustments. (Strong) *CYP2D6* extensive metabolizer: • For normal metabolism of tricyclics, initiate therapy with recommended starting dose. (Strong) *CYP2D6* intermediate metabolizer: • For reduced metabolism of tricyclics to less active compounds as compared with extensive metabolizers, consider a 25% reduction of recommended starting dose. Use TDM to guide dose adjustments. (Moderate) *CYP2D6* poor metabolizer: • For greatly reduced metabolism of tricyclics to less active compounds as compared with extensive metabolizers, avoid tricyclic use due to potential side effects. Consider alternative drug not metabolized by *CYP2D6*. (Strong) • If a tricyclic is warranted, consider a 50% reduction of recommended starting dose. Use TDM to guide dose adjustments. (Strong) Dosing recommendations for amitriptyline based on *CYP2C19* phenotype:	No recommendations	4.9 – Fair (recommendations based on CV evidence and consensus; methods evaluation of bias and interpretation not described; guideline not reviewed by external experts)

Sponsor, Year	Guideline Title	Relevant Recommendations		Quality/Main Limitations
		Pharmacogenomic Testing	Repeat Testing	
		CYP2C19 ultrarapid metabolizer: • For increased metabolism of amitriptyline as compared with extensive metabolizers, consider alternative drug not metabolized by *CYP2C19*. If tricyclic is warranted, use therapeutic drug monitoring to guide dose adjustments. (Optional) *CYP2C19* extensive metabolizer: • For normal metabolism of amitriptyline, initiate therapy with recommended starting dose. (Strong) *CYP2C19* intermediate metabolizer: • For reduced metabolism of amitriptyline as compared with extensive metabolizers, initiate therapy with recommended starting dose. (Strong) *CYP2C19* poor metabolizer: • For greatly reduced metabolism of amitriptyline as compared with extensive metabolizers, consider a 50% reduction of recommended starting dose. Use TDM to guide dose adjustments. (Moderate)		
CPIC (Hicks et al., 2015)	*Clinical Pharmacogenetics Implementation Consortium Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Selective Serotonin Reuptake Inhibitors*	Dosing recommendations for paroxetine based on CYP2D6 phenotype: *CYP2D6* ultrarapid metabolizer: • For increased metabolism to less active compounds when compared with extensive metabolizers, select an alternative drug not predominantly metabolized by *CYP2D6*. (Strong) *CYP2D6* extensive metabolizer: • For normal metabolism, initiate therapy with recommended starting dose. (Strong) *CYP2D6* intermediate metabolizer: • For reduced metabolism when compared with extensive metabolizers, initiate therapy with recommended starting dose. (Moderate) *CYP2D6* poor metabolizer: • For greatly reduced metabolism when compared with extensive metabolizers, selective an alternative drug not predominantly metabolized by *CYP2D6* or if paroxetine is warranted, consider a 50% reduction of recommended starting dose and titrate to response. (Optional) Dosing recommendations for fluvoxamine based on *CYP2D6* phenotype:	No recommendations	4.9 – Fair (recommendations based on CV evidence and consensus; methods for evaluation of bias and interpretation not described; guideline not reviewed by external experts)

Sponsor, Year	Guideline Title	Relevant Recommendations		Quality/Main Limitations
		Pharmacogenomic Testing	Repeat Testing	
		CYP2D6 ultrarapid metabolizer: • No recommendation due to lack of evidence. *CYP2D6* extensive metabolizer: • For normal metabolism, initiate therapy with recommended starting dose. (Strong) *CYP2D6* intermediate metabolizer: • For reduced metabolism when compared with extensive metabolizers, initiate therapy with recommended starting dose. (Moderate) *CYP2D6* poor metabolizer: • For greatly reduced metabolism when compared with extensive metabolizers, consider a 25%-50% reduction of recommended starting dose and titrate to response or use an alternative drug not metabolized by *CYP2D6*. (Optional) Dosing recommendations for citalopram and escitalopram based on *CYP2C19* phenotype: *CYP2C19* ultrarapid metabolizer: • For increased metabolism when compared with extensive metabolizers, consider an alternative drug not predominantly metabolized by CYP2C19. (Moderate) *CYP2C19* extensive metabolizer: • For normal metabolism, initiate therapy with recommended starting dose. (Strong) *CYP2C19* intermediate metabolizer: • For reduced metabolism when compared with extensive metabolizers, initiate therapy with recommended starting dose. (Strong) *CYP2C19* poor metabolizer: • For greatly reduced metabolism when compared with extensive metabolizers, consider a 50% reduction of recommended starting dose and titrate to response or select an alternative drug not predominantly metabolized by *CYP2C19*. (Moderate) Dosing recommendations for sertraline based on *CYP2C19* phenotype: *CYP2C19* ultrarapid metabolizer:		

Sponsor, Year	Guideline Title	Relevant Recommendations		Quality/Main Limitations
		Pharmacogenomic Testing	Repeat Testing	
		• For increased metabolism when compared with extensive metabolizers, initiate therapy with recommended starting dose. If patient does not respond to recommended maintenance dosing, consider alternative drug not predominantly metabolized by *CYP2C19*. (Optional) *CYP2C19* extensive metabolizer: • For normal metabolism, initiate therapy with recommended starting dose. (Strong) *CYP2C19* intermediate metabolizer: • For reduced metabolism when compared with extensive metabolizers, initiate therapy with recommended starting dose. (Strong) *CYP2C19* poor metabolizer: • For greatly reduced metabolism when compared with extensive metabolizers, consider a 50% reduction of recommended starting dose and titrate to response or select an alternative drug not predominantly metabolized by *CYP2C19*. (Optional)		

*According to the Rigor of Development domain of the Appraisal of Guidelines Research and Evaluation (AGREE) tool, along with a consideration of commercial funding and conflicts of interest among the guideline authors. Guidelines were scored on scale of 1 to 7 and judged to be good (6-7), fair (4-5), or poor (1-3).