ISPG Pharmacogenetic Testing Statement

Daniel Mueller, MD, PhD

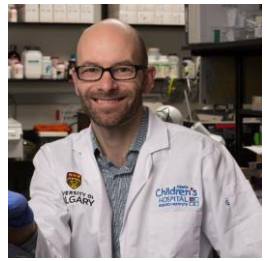
Centre for Addiction and Mental Health

University of Toronto

Chad Bousman, MPH, PhD

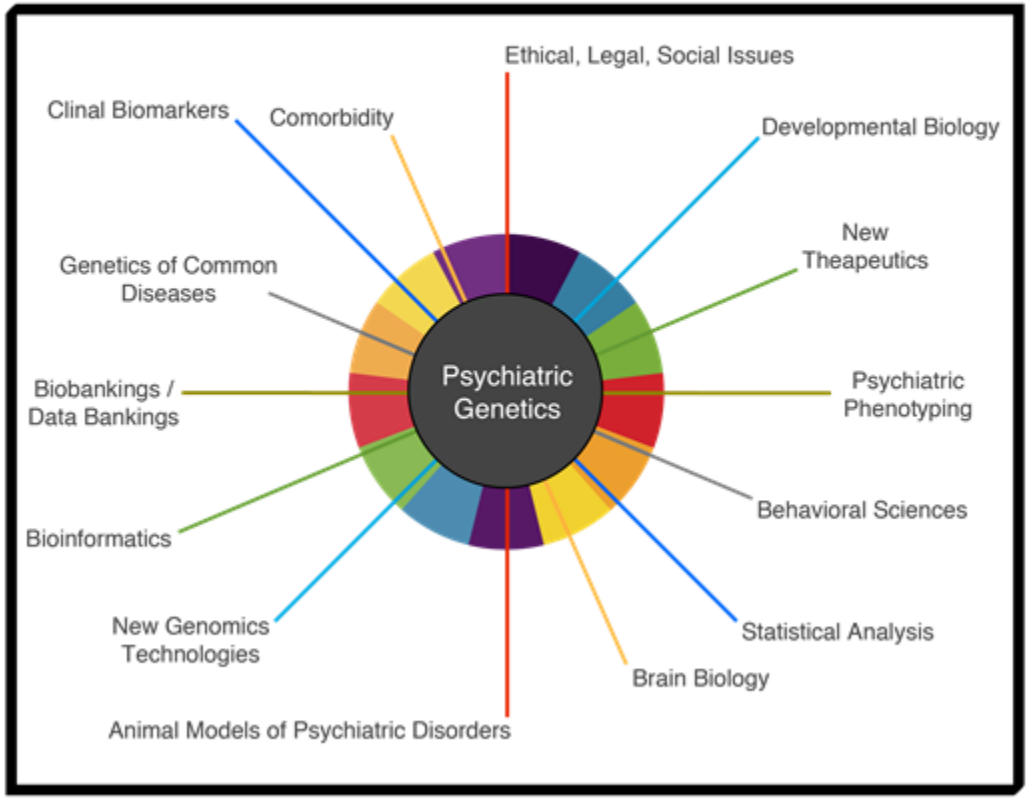
Department of Medical Genetics

University of Calgary



ISPG VISION STATEMENT

(www.ispg.org)



- Facilitating research in the genetics of psychiatric disorders (including substance use disorders) and allied traits.
- **Promoting education in psychiatric genetics, both for the scientific community and for the lay public.**
- Guiding early career researchers interested in the field of psychiatric genetics.
- Encouraging communication and collaboration between researchers in this area.
- **Striving for the highest scientific and ethical standards in research and clinical practice.**
- Paving the way to alleviate suffering due to psychiatric disorders.

A Brief History of the ISPG and the Statement

Brief History:

1986 – 1992: ISPG founded, since then annual meetings (~700 attendees)

2013 – Genetic Testing Taskforce founded

2014 – First Genetic Testing Statement Published

2019 – Updated Genetic Testing Statement Published

ISPG Genetic Testing Committee:

70 members (clinicians, scientists, healthcare administrators)

4 domains:

1) Genetic Tests to Assist Diagnosis and Characterize Risk;

2) Reporting of Incidental or Secondary findings;

3) Psychological, ethical and clinical implications in genetic testing; and

4) Pharmacogenetic Tests to Guide Optimal Treatment

Purpose:

To provide recommendations for clinicians in the public to consider

(Pharmaco-)Genetic Testing Statement 2014

Genetic Tests to Guide Optimal Treatment

There is a growing list of genetic markers associated with effectiveness and adverse events of various drugs. In some situations, pharmacogenetic markers can supplement clinical information to help guide treatment decisions for psychiatric disorders, reducing the risk of treatment failure and serious adverse events. For example, in patients of Asian ancestry who receive carbamazepine, the HLA-B*1502 marker substantially increases risk of serious skin disorders (Stevens Johnson Syndrome and toxic epidermal necrolysis; ref 7).

Some CYP450 enzymes (e.g., CYP2D6, CYP2C19) are highly involved in metabolism of drugs, including antidepressants and antipsychotics. Variation in the genes that encode these enzymes can lead to differences in drug metabolism that can be predicted by genetic markers. Individuals with genetic markers of poor or rapid metabolism may be at higher risk for non-response, adverse events, or drug-drug interactions. In view of these findings, expert panels have started to publish guidelines for use of CYP450 testing in psychiatry (ref 8). We generally concur with these guidelines, which do not recommend genetic testing on a global level, but provide guidance if genotype data are already available. Other gene-drug pairings are under active investigation. In addition, other factors that influence drug outcome (such as diet, use of other medications, or

treatment resistance) need to be taken into account and studied further. Randomized, double blind clinical trials are needed to establish the clinical utility of genetic testing in psychiatric drug treatment. We recommend clinicians follow good medical practice and stay current on changes to drug labeling and adverse event reports. One useful (but not necessarily exhaustive) list of pharmacogenetic tests is maintained by the US Food and Drug Administration (ref 9).

4. Agencies such as the US FDA have begun to include pharmacogenomic information in drug labeling and recommend genetic testing for some specific psychiatric drugs. We suggest clinicians consider such recommendations in treatment decisions.

5. Evidence remains inconclusive as to the possible clinical utility of CYP450 genetic testing in psychiatry, but more research is needed.

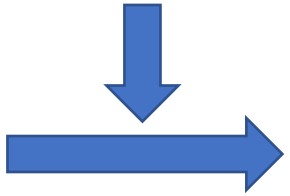
Overview of the Process – Part 1

Original Statement

PubMed PharmGKB The Pharmacogenomics Knowledgebase

CPIC Clinical Pharmacogenetics Implementation Consortium KNMP

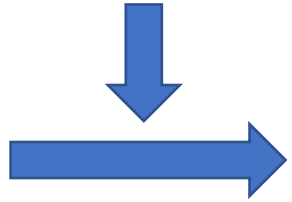
Resources



1st Draft of Revised Statement
(Daniel & Chad)

Google docs

Subcommittee Deliberations



Subcommittee Consensus Reached

Committee Deliberations: Key Discussion Points

Perceptions of the Evidence

"..there is little (any?) actual published evidence that testing for these variants and utilising the information does actually result in the expected improved outcomes."

".. we lack solid evidence of the clinical utility of genetic testing for any psychotropic, with the sole exception of HLA testing prior to carbamazepine in patients of Asian ancestry.

"research indicates that genetic tests are promising to help define the best treatment, but definite, large, peer-reviewed studies have not been published."

Committee Deliberations: Key Discussion Points

Perceptions of the Evidence

Perspectives on the Evidence Required

"..what type of evidence is or should be needed to allow us to make such a recommendation. Would an RCT be necessary?"

"I think we should say more trials are needed."

Are Randomized Controlled Trials Necessary to Establish the Value of Implementing Pharmacogenomics in the Clinic?

Rachel Huddart[1], Katrin Sangkuhl[1], Michelle Whirl-Carrillo[1] and Teri E. Klein[1,2,*]

Received February 1, 2019; accepted February 22, 2019. doi:10.1002/cpt.1420

Committee Deliberations: Key Discussion Points

Perceptions of the Evidence

Perspectives on the Evidence Required

Clinical Perspectives on PGx Testing

"…the clinicians I know essentially never carry out genetic testing and it seems a bit much to claim that they are all negligent, especially if we don't have really strong evidence to back that up."

"I think there is a significant risk that insisting on genetic testing before starting antidepressant treatment will at minimum be burdensome for doctors and patients but more importantly will actually result in some patients not receiving treatment."

Committee Deliberations: Key Discussion Points

Perceptions of the Evidence | **Perspectives on the Evidence Required** | **Clinical Perspectives on PGx Testing** | **Clinical Validity vs. Clinical Utility**

"Saying that testing could predict somebody to be at higher risk of side effects and hence be prescribed a lower dose is not evidence that testing actually produces benefit."

"There are potential negative consequences to testing, especially outside of centres of excellence. For example, one disadvantage is that it introduces a delay between seeing and assessing the patient and starting treatment."

Recommendation – First Version

- Pharmacogenomic testing results for CYP2D6, CYP2C19, HLA-A, and HLA-B are valuable for reducing the risk for poor response or adverse events. When this information is available, providers are strongly encouraged to integrate this information in their medication selection and dosing decisions in alignment with pharmacogenomic recommendations advanced by regulatory agencies, such as the US Food and Drug Administration, and expert groups, such as the Clinical Pharmacogenetics Implementation Consortium (CPIC).

Overview of the Process – Part 2

Original Statement

PubMed PharmGKB The Pharmacogenomics Knowledgebase CPIC Clinical Pharmacogenetics Implementation Consortium KNMP

Resources

Google docs

Subcommittee Deliberations

DRAFT

1st Draft of Revised Statement
(Chad & Daniel)

Subcommittee Consensus Reached

ISPG Board Review

Board Rejects

REJECTED

Committee Revision

ISPG Board Feedback

1. **Concerns about Industry Involvement in CPIC Guidelines**
2. **Genes of focus: Yea: HLA Nay: CYP2D6 & CYP2C19**

Rejected by Board:

- "Pharmacogenomic testing results for CYP2D6, CYP2C19, HLA-A, and HLA-B are valuable for reducing the risk for poor response or adverse events"

Board's Suggested Revision:

- "Other genes, such as CYP2D6, CYP2C19, affect the metabolism of many drugs, but their clinical utility in psychiatry remains unproven."

Committee Revision:

- "Genetic information for CYP2C19 and CYP2D6 would likely be most beneficial for individuals who have experienced an inadequate response or adverse reaction to a previous antidepressant or antipsychotic trial."

Overview of the Process

Resources

Subcommittee Deliberations

~10 Months from initiation to approval

ittee eached

ISPG Board Review

Board Rejects

Committee Revision

Board Approved

Recommendation - Approved Version

Pharmacogenetic testing should be viewed as a decision-support tool to assist in thoughtful implementation of good clinical care. We recommend HLA-A and HLA-B testing prior to use of carbamazepine and oxcarbazepine, in alignment with regulatory agencies and expert groups. Evidence to support widespread use of other pharmacogenetic tests at this time is still inconclusive, but when pharmacogenetic testing results are already available, providers are encouraged to integrate this information into their medication selection and dosing decisions. Genetic information for CYP2C19 and CYP2D6 would likely be most beneficial for individuals who have experienced an inadequate response or adverse reaction to a previous antidepressant or antipsychotic trial.

https://ispg.net/genetic-testing-statement/

Key lessons learned…

- While ISPG is the leading society in psychiatric genetics, psychiatric pharmacogenetics has traditionally played a relatively minor role.
- Thus, many scientists are also not aware of the science behind and many have not heard much about PharmGKB and CPIC before
- Reaching consensus means to find compromises – with the risk that noone leaves being happy
- Reaching consensus is particualrly difficult, if new members enter the process later in the game as they have missed previous discussions (including the ISPG Board)
- The discussion gets regularly confounded by critical attitudes surronding commercial test panels (Quote: Tests are all the same)

Acknowlegments

- Andrea Gaedigk
- Teri Klein
- Kathrin Sangkuhl
- Francis McMahon
- Margit Burmeister
- Juergen Deckert
- Steve Potkin
- Lynn DeLisi
- ...and many more!