

Pharmacogenomic Testing for Psychiatric Medications for Children and Adolescents

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The Purpose of Pharmacogenomic Testing

- Leveraging individual gene variations in medication metabolism or drug targets to predict treatment response and, potentially, guide treatment selection
- Improve the possibility that a specific medication will provide the best therapeutic benefit with the least adverse effects
- Early pharmacogenomic tests focused on CYP2D6 and CYP2C19 individually
- Newer tests use “combinatorial” strategies that rely on algorithms that evaluate genotypes for a series of genes
- Generally considered to be most useful when a patient has had significant side effects to low-moderate doses of medication or has been non-responsive to several medications

Ethnic Variability in Select CYP450 Isoenzymes

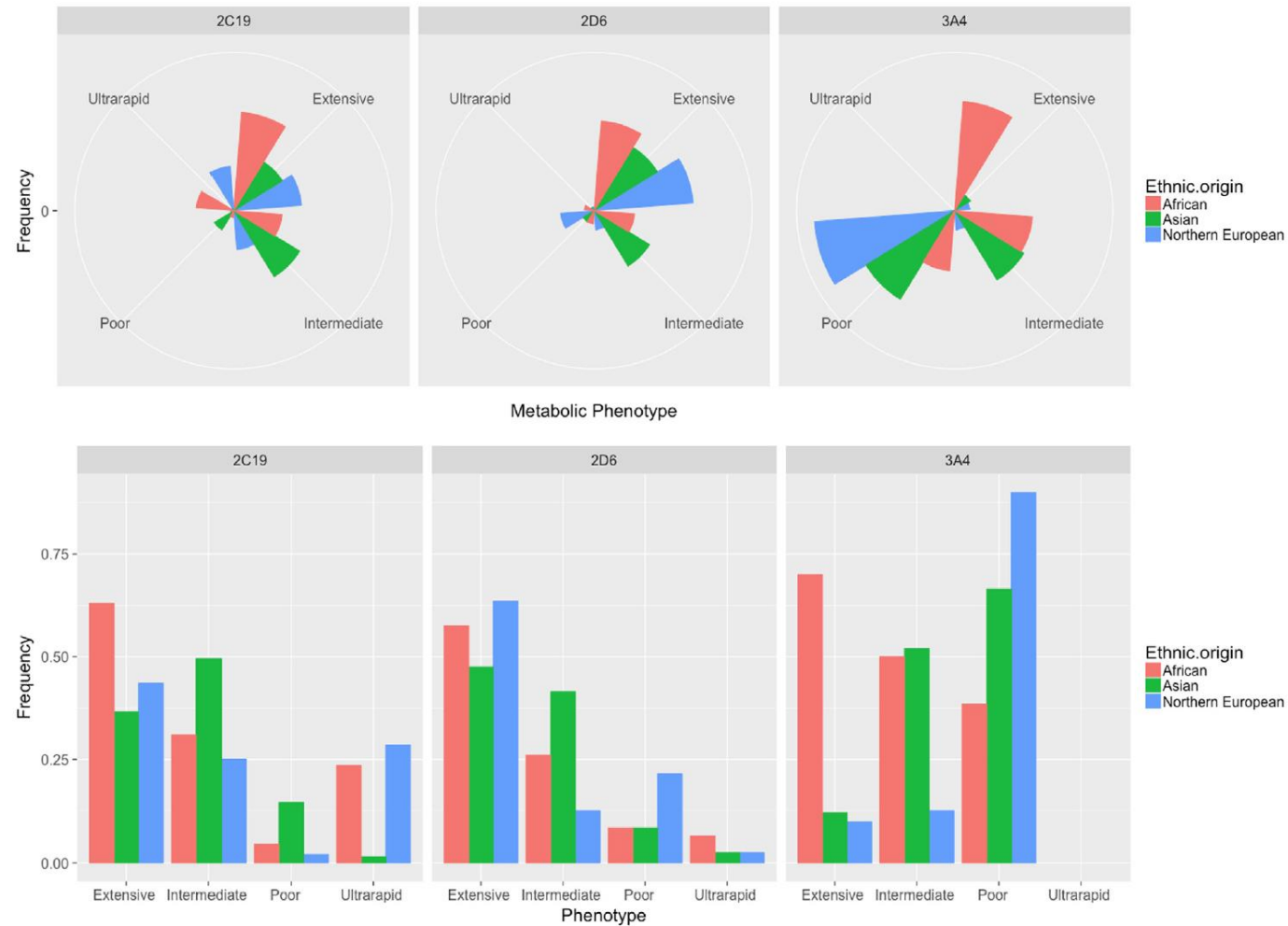
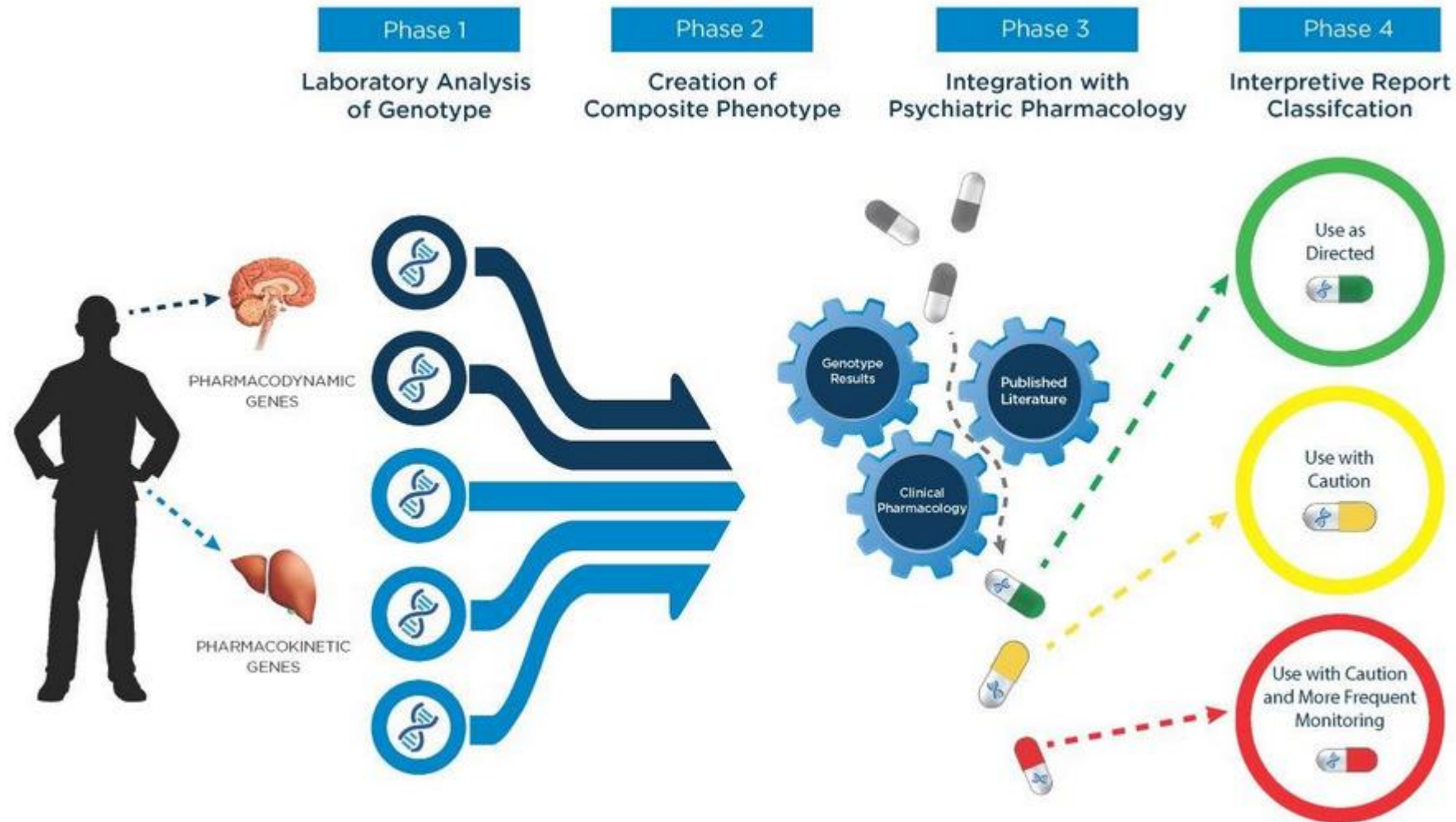
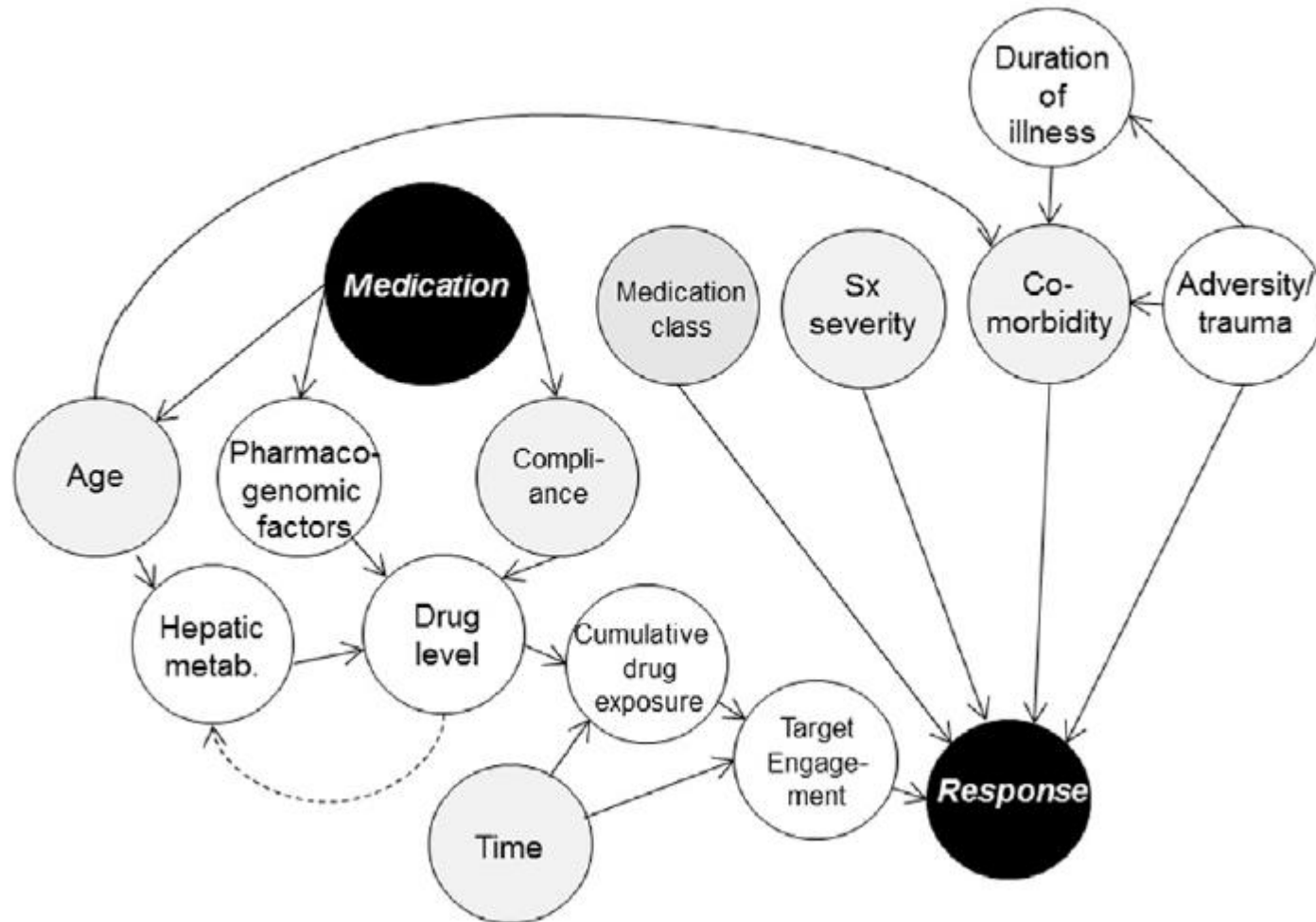


FIG 1. Ethnic variability in CYP450 Phenotypes. Allelic frequencies for phenotypes of 2C19, 2D6 and 3A4 vary across ethnic groups, which may inform testing. These variations are presented for the following ethnicities: (1) African, (2) Asian, and (3) Northern Europeans (blue). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

“Combinatorial” Pharmacogenomics



Pharmacogenomics is only a piece of the medication choice puzzle



Guidelines are based on adult evidence base

- Most studies of SSRI pharmacogenomics are done in adults with MDD
- Translation across ages and to other disorders is not clear
- Significant differences between adult and pediatric patients in the frequency and magnitude of side effects to these medications
- These differences may be due to the activity of drug metabolizing enzymes that change through development
- There is no current requirement for counseling before or after pharmacogenomic testing
- Patients/parents may be disappointed if they believe that this testing will definitively find the best medication or be at risk of misinterpreting results
- Pharmacogenomic testing is just one factor to consider

GUIDED Study

- Genomics Used to Improve Depression Decisions (GUIDED)
- N = 1167 adults with MDD and an inadequate response to at least one antidepressant
- Treatment as usual (TAU) or pharmacogenomics-guided intervention
- Primary outcome – symptom improvement by week 8 on the HAM-D
- Secondary outcomes – response ($\geq 50\%$ reduction of symptoms) or remission (score ≤ 7 on the HAM-D)
- Results:
 - Improvement was not better with pharmacogenomic-guided intervention vs TAU (did not meet primary outcome)
 - More patients responded or remitted when switched to the treatment guided by the pharmacogenomic intervention (did meet secondary outcome)

FDA Safety Communication

October 2018

- Direct-to-consumer tests (e.g., 23andme)
- FDA permits marketing
- Tests are accurate and can correctly identify 33 genetic variants
- Approval only for adults > 18 years
- Should not change or stop any medications based on test results
- Confirm with independent testing
- Allows for FDA oversight

November 2018

- Safety communication
- Cautions clinicians and patients that no current test is FDA-approved
- May lack clinical evidence supporting use
- Any change in treatment based upon test results may lead to inappropriate treatment decisions and serious health consequences

DTC vs Clinical Testing

- DTC = tests like 23andme (public domain)
- Clinical testing – tests like GeneSight and GeneMind
- After FDA Safety Communication, companies that provide “combinatorial” pharmacogenomic testing, like GeneSight, put out statements that they were “clinical” testing, not DTC
- The FDA has not approved any pharmacogenomic testing, either DTC or clinical
- In August 2019, the FDA asked Myriad Genetics (GeneSight) for further data because the relationship between genetic variations and medication effects has not been established.

Does Indiana Medicaid cover pharmacogenomic testing

- It may, under medical billing
- Prior authorization (PA) is required for all genetic testing
- Documentation required:
 - Medical necessity, specifically stating the impact on treatment
 - Genetic counseling has been performed
- The following will NOT be covered:
 - Sole convenience of information for the patient without impacting treatment
 - Medical management of family members
 - All screening tests
 - If a genetic test has been previously performed and provides a conclusive diagnosis
- Coverage is limited to once per member per lifetime

Organization Statements on Pharmacogenomic Testing

- FDA:
 - The FDA has not authorized any DTC pharmacogenomic tests that predict whether a person is likely to respond to or have adverse events from any specific drug
- American Psychiatric Association:
 - Pharmacogenetic testing is promising, but not ready for widespread use
- International Society of Psychiatric Genetics:
 - Does not endorse the use of pharmacogenomics in practice; clinicians should follow good medical practice and stay current on changes in drug labeling and adverse event reports

Summary

- Pharmacogenomic testing holds promise, but the evidence base does not yet support clinical use for every patient
- Most studies with large enough numbers of participants and good study design have been done with adults
- Adult study results cannot be translated to child and adolescent patients due to significant differences in metabolism and receptors that may change over time
- Clinically, pharmacogenomic testing is best considered if a patient has not responded to several medications in a drug class (is considered treatment-resistant) or has significant side effects to low-moderate doses of medications that are not expected.
- Some private insurers have begun to cover pharmacogenomic testing, but prior authorization processes are required within Medicaid.

References

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