A PSYCHIATRIST'S PERSPECTIVE ON GENETIC TESTING FOR PSYCHIATRIC MEDICATIONS IN THE WAKE OF APA TASK FORCE RECOMMENDATIONS

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LEARNING OBJECTIVES

- INTRODUCTION TO PHARMACOGENOMICS
- APA TASK REVIEW
- RESEARCH REVIEW
- COMMERCIAL CLAIMS ANALYSIS
- EVIDENCE GAP HIGHLIGHT
- THE SCIENCE OF THE ART OF PSYCHOPHARMACOTHERAPY

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INTRODUCTION TO PHARMACOGENOMICS:

Pharmacogenomics is the study of how genes influence an individual's response to drugs. This field is a subset of genomics that deals specifically with the interactions between therapeutics and the genetic makeup of individuals.

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APA TASK FORCE REVIEW

An APA Task Force for Novel Biomarkers and Treatments looked at claims of four major commercial companies offering genetic testing to improve medication choices and reduce trial and error.

The Task Force concluded there is not sufficient information to support the widespread use of pharmacogenetic testing in clinical practice.

APA TASK FORCE REVIEW

Task Force examined **GeneSight, GeneCept, IDgenetix, and CNSDose**. The Task Force examined the evidence behind the claims that these pharmacogenetic tests can enhance the accuracy of drug prescriptions and reduce the trial and error often associated with treating psychiatric disorders.

Their findings highlighted several critical issues:

1.Methodological Flaws: The research supporting the claims of these companies often had methodological flaws that seriously undermined the claims. This includes issues like small sample sizes, short study durations, and lack of proper blinding in trials.

2.Lack of Transparency: The algorithms used by these companies to derive treatment recommendations from genetic tests are exclusive. This lack of transparency prevents independent verification of the claims and raises concerns about the scientific validity of the advice provided.

3.Insufficient Evidence: Ultimately, the Task Force concluded that there is not enough robust evidence to support the widespread clinical use of these pharmacogenetic tests. They noted that the data does not convincingly support the commercial claims of improved treatment efficacy through these tests.

APA TASK FORCE REVIEW

The conclusion drawn by the APA Task Force is that while the concept of using genetic testing to guide antidepressant prescriptions is promising, the current applications by these commercial entities do not yet meet the high standards required for widespread clinical use. They emphasized the need for more rigorous, transparent, and independently verifiable research to substantiate the claims made by pharmacogenetic testing companies.

This cautious stance reflects a broader consensus in the psychiatric community that while pharmacogenetics holds potential for the future of personalized medicine, it is not yet ready to be implemented widely without further validation and evidence of clinical utility.

RESEARCH REVIEW

- GENOME-WIDE PHARMACOGENETIC STUDIES HAVE BEEN UNDERTAKEN TO SYSTEMATICALLY INVESTIGATE GENE-BY-DRUG INTERACTIONS.

- AMONG THE LARGEST ARE THE GENOME-BASED THERAPEUTIC DRUGS FOR DEPRESSION (GENDEP) PROJECT, THE MUNICH ANTIDEPRESSANT RESPONSE SIGNATURE (MARS) PROJECT, AND THE SEQUENCED TREATMENT ALTERNATIVES TO RELIEVE DEPRESSION (STAR*D).

- UNFORTUNATELY, A META-ANALYSIS OF DATA FROM ALL THREE INITIATIVES DID NOT REVEAL RELIABLE PREDICTORS OF TREATMENT OUTCOMES SEVERAL RECENT REVIEWS ADDRESS BOTH THE PROMISE AND THE CHALLENGE OF USING PHARMACOGENETIC DATA TO IMPROVE PRECISION IN TREATING MAJOR DEPRESSION. FEW ACTIONABLE DRUG-GENE INTERACTIONS HAVE BEEN IDENTIFIED, WITH AN EXCEPTION BEING THE HUMAN LEUKOCYTE ANTIGEN (HLA) *B-1502 ALLELE, WHICH STRONGLY ASSOCIATES WITH CARBAMAZEPINE-INDUCED STEVENS-JOHNSON SYNDROME AMONG HAN CHINESE.

RESEARCH REVIEW

- INSTEAD, IT HAS BEEN GENERALLY CONCLUDED THAT DESPITE LAUDABLE EFFORTS, NO STUDIES HAVE LED TO ACTIONABLE PHARMACOGENETIC DATA THAT PROVIDE A MORE COMPREHENSIVE FRAMEWORK FOR SELECTION OF INITIAL ANTIDEPRESSANT MEDICATIONS OR TO GUIDE SUBSEQUENT STEPS IN THE TREATMENT OF MAJOR DEPRESSION.

- BECAUSE MOST PRESCRIBERS OF ANTIDEPRESSANTS ARE NOT EXPERTS IN PHARMACOGENOMICS OR GENOMICS, THE APA TASK FORCE FOR BIOMARKERS AND NOVEL TREATMENTS CONDUCTED A DETAILED ANALYSIS OF THE LITERATURE TO PROVIDE PRESCRIBERS WITH A READILY UNDERSTANDABLE SUMMARY OF THE FIELD, ESPECIALLY IN VIEW OF EFFORTS TO MARKET THESE TESTS TO PSYCHIATRISTS, PRIMARY CARE PHYSICIANS, AND THE PUBLIC.

On the Marketing and Use of Pharmacogenetic Tests for Psychiatric Treatment

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Clinicians hope to see translational uses of powerful new technologies, such as brain imaging and genomic testing, guiding care of patients. In genomics, many newly risen companies promise to address this hope by vigorously marketing pharmacogenetic (Pgen) tests, especially for the treatment of major depressive disorder (MDD). One company's website reports sales of over 650 000 Pgen tests.[1] Does the evidence support such use? The heterogeneous and complex underlying causes and mechanisms of illness and clinical response to treatment in MDD strongly suggest that there will be serious issues limiting or preventing the development of Pgen approaches to treatment choice. Simply put, MDD is determined by a large number of genes, and, except in rare cases, no single gene or limited gene set, even those for drug metabolism and drug targets, determines more than a few percent of the risk of illness or course of treatment.[2-4] Environmental factors (age, sex, diet, alcohol use, hormonal status, general health) and comedication are usually more important factors than inherited determinants of drug metabolism and response.[5] While the activity of metabolic enzymes is heritable, extremely rapid or slow metabolism is rare, and dosing needn't be guided by Pgen rather than by careful dose choice and monitoring therapeutic and adverse effects.[6] Thus, the available evidence suggests that Pgen tests will not contribute much to care.

COMMERCIAL CLAIM ANALYSIS

In the analysis of commercial claims made by companies marketing genetic tests for improving psychiatric medication selection, several critical considerations emerge:

1. Overstated Efficacy: Companies often promote these genetic tests with claims that they can significantly reduce the trial-and-error process of finding the right psychiatric medication. However, the scientific backing for such claims is frequently questioned by experts. The evidence provided is sometimes based on studies with small sample sizes, short durations, or methodological flaws that may not adequately support the broad claims of improved clinical outcomes.

2. Lack of Transparency: A major concern is the proprietary nature of the algorithms used to generate patient-specific recommendations. The lack of transparency in how these recommendations are derived makes it difficult for the medical community to evaluate and validate the effectiveness and reliability of these tests. This secrecy also complicates peer reviews and unbiased evaluations.

3. Regulatory Scrutiny: Although some tests have received clearance or approval from regulatory bodies like the FDA, others have not, and the regulatory landscape is uneven. This inconsistency can lead to confusion among healthcare providers and patients about the reliability and validity of these tests.

COMMERCIAL CLAIM ANALYSIS

4. Ethical and Privacy Concerns: The use of genetic data raises significant ethical and privacy issues. There is concern about how this sensitive information is stored, who has access to it, and how it might be used beyond the scope of medication selection. Patients and providers must be aware of these issues and consider them when deciding whether to use these tests.

5. Cost vs. Benefit: The cost of pharmacogenetic testing can be high, and it is not always covered by insurance. This raises questions about the cost-effectiveness of such tests, particularly if the benefits are not substantially better than traditional methods of selecting medications based on clinical judgment and Psychosocial Approach.

For instance IDgenetix test cost: $330 out of pocket for commercial insurance or uninsured. It cost $0 out of pocket for Medicare Part B, Medicare Advantage and Medicaid (subject to deductible amounts).

EVIDENCE GAP HIGHLIGHT

There's a notable gap between the theoretical potential of these tests and the actual evidence that supports their routine clinical use. This discrepancy is significant.

While the potential of genetic testing in psychiatry is substantial, bridging the gap between this potential and practical, evidence-based clinical application requires more robust research, clearer regulatory guidelines, and broader educational efforts within the medical community. Stakeholders must address these issues collaboratively to harness the full capabilities of pharmacogenetics in improving mental health outcomes.

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The science of the art of psychopharmacotherapy:

Medication outcome are shaped by a range of psychosocial factors:

Prescriber effects

Characteristics of the pill

Non-clinical patient characteristics

Therapeutic alliance

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PILL CHARACTERISTICS SHAPE OUTCOME:

Characteristics of the pill–Color (de Craen & Roos, et al, 1996; Fisher & Greenberg, 1997)
Red pills are energizing
Blue pills calming… in most cases (Cattaneo, et al 1970)
Expensive pills work better (Waber & Shiv, et al, 2008) •
Implications for generic substitution–Most patients report decreased intention to continue medications (Roman, 2009)
34% of patients experience new adverse events (Weissenfeldet al, 2010).

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- **PLACEBO AND ANTIDEPRESSANT EFFECTS**
- • PLACEBO EFFECTS ACCOUNT FOR A LARGE PORTION OF ANTIDEPRESSANT RESPONSE.
- • USING UNBIASED FDA DRUG STUDY DATABASE, INCLUDING UNPUBLISHED STUDIES ⇢ • ~75-81% OF DRUG RESPONSE IS DUE TO THE PLACEBO EFFECT (KIRSCH & SAPIRSTEIN, 1998; KAHN, ET AL, 2000; KIRSCH, ET AL, 2002)

Non-clinical patient characteristics:

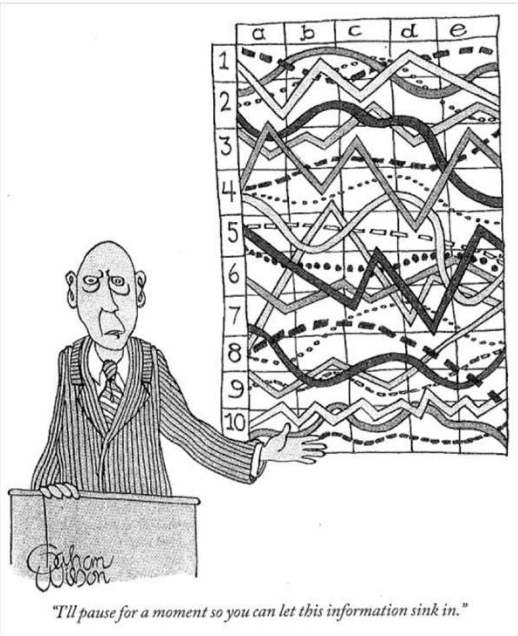
- **Socioeconomic Status**: This can include income, education level, and occupation, which might affect a patient's access to healthcare services and their ability to adhere to treatment plans.
- **Cultural Background**: Cultural beliefs and practices can influence how patients perceive illness and treatment, their preferences for certain types of healthcare interventions, and how they communicate their symptoms.
- **Lifestyle Choices**: This encompasses diet, physical activity, smoking, alcohol consumption, and other behaviors that can impact health but are not clinical symptoms themselves.
- **Psychosocial Factors**: Includes stress levels, social support networks, family dynamics, and other psychological or social conditions that might affect a person's overall health and well-being.
- **Geographic Location**: Living in a rural vs. urban area, climate, and local environmental conditions can also influence health outcomes and healthcare access.

"NON-CLINICAL" PATIENT VARIABLES AFFECT MEDICATION OUTCOMES

- Neuroticism (Joyce & Paykel, 1989; Scott et al, 1995; Bagby et al, 2002; Steunenberg et al, 2010)
- Defensive style (Kronström et al., 2009)
- Locus of control (Reynaert et al, 1995)
- Autonomy (Peselow et al, 1992)
- Sociotropy (Peselow et al, 1992)
- Social disadvantage (Hahn, 1997)
- Acquiescence (McNair et al., 1968, 1970; Fast & Fisher, 1971)
- Attachment style (Ciechanowski et al., 2001, 2006; Comninos & Grenyer, 2007)
- Early Trauma (Williams et al, 2016)

- Expectations of treatment (Meyer et al., 2002; Krell et al, 2004; Aikens et al, 2005; Gaudiano & Miller, 2006; Sneed et al., 2008)
- Treatment preference (Lin et al., 2005; Iacoviello et al, 2007; Kocsis et al, 2009; Raue et al, 2009; Kwan, Dimidjian & Rizvi, 2010)
- Ambivalence about medications (Sirey et al, 2001; Aikens et al, 2008; Warden et al, 2009)
- Secondary gains associated with illness (van Egmond & Kummeling, 2002)
- Autonomous motivation for treatment (Zuroff & Koestner, et al, 2007)
- Readiness to change (Beitman et al, 1994; Lewis & Simons, et al, 2009)

- Theory of Illness (Sullivan, 2001)



"I'll pause for a moment so you can let this information sink in."

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PHARMACOTHERAPY ALLIANCE:

Alliance is not the same as compliance
Alliance directly correlated with treatment response (Krupnick et al, 1996)
Alliance is an equally powerful factor in pharmacotherapy as in psychotherapy
Alliance is a stronger determinant of treatment outcome than drug condition (active drug vs. placebo)

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- **ELEMENTS OF AN EFFECTIVE PHARMACOTHERAPEUTIC ALLIANCE:**

- WARMTH & PRESENCE
- AUTONOMY SUPPORT
- AGREEMENT ABOUT TARGETS
- RESPECT FOR TREATMENT PREFERENCES
- SHARED DECISION-MAKING
- GOOD COMMUNICATION

SUMMARY

Challenges and Limitations:

- **Insufficient Evidence**
- **Lack of Transparency**
- **Regulatory and Ethical Concerns**
- **Economic and Accessibility Issues**

Genetic testing for psychiatric medications is currently not the standard of care (defined by FDA and APA).

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SUMMARY

Research Needs: Further research is crucial to establish the validity and utility of pharmacogenetic testing in psychiatry. Large-scale, well-designed clinical trials are needed to conclusively demonstrate that genetic testing can improve treatment outcomes compared to current standard care practices. Additionally, studies should also focus on the economic benefits of these tests, examining whether they can truly provide cost savings by reducing ineffective prescribing and minimizing side effects.

Conclusion: The consensus among psychiatrists that pharmacogenetic testing is not yet ready for standard care stems from these challenges and limitations. While the potential for personalized medicine in psychiatry is immense, current genetic tests must be subjected to rigorous scrutiny and validation. The field requires continued research, clearer regulatory guidelines, and greater transparency from commercial providers to ensure that when pharmacogenetic tests are used, they are both scientifically sound and clinically relevant.

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REFERENCES

- **Hall-Flavin et al., 2013:** A study showing significant improvement in antidepressant response when pharmacogenetic information (e.g., CYP2D6, CYP2C19) was used for dosing, compared to standard treatment. Highlighted in a meta-analysis by Bousman et al., 2019. Frontiers in Psychiatry
- **Jukic et al., 2018:** Found that patients with specific CYP2C19 genotypes were more likely to switch from escitalopram due to poor efficacy, suggesting genetic testing could guide more effective medication choices. MDPI Pharmaceuticals
- **GeneCept, IDgenetix, CNSDose, and ABCB1:** Reviewed in a study assessing the effectiveness of pharmacogenetic decision support tools, noting improvements in medication adherence and cost savings (GeneCept and IDgenetix), and better treatment outcomes (CNSDose and ABCB1). However, more research and genetic variant inclusion are necessary. Education in Psychiatry
- **APA Task Force for Novel Biomarkers and Treatments:** Critiqued the claims of four major genetic testing companies (GeneSight, GeneCept, IDgenetix, CNSDose), pointing out insufficient evidence, methodological flaws, and lack of transparency in commercial genetic tests. Psychiatric News, APA
- **Bousman et al., 2021:** Conducted studies published in *Pharmacopsychiatry* and the *Canadian Journal of Psychiatry*, highlighting the potential of pharmacogenetic testing to enhance treatment precision in psychiatry by matching patients with the most suitable medications based on their genetic profile. These studies provide further evidence supporting the integration of pharmacogenetics into clinical practice. Pharmacopsychiatry, Canadian Journal of Psychiatry.

- **Bousman & Hopwood, 2016:** Discussed in *The Lancet Psychiatry*, this study explores the implications of pharmacogenetic testing in clinical settings, emphasizing the potential for these tools to significantly improve the management of psychiatric disorders by tailoring treatments to individual genetic profiles. The Lancet Psychiatry

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Q&A

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