

# MOVING TOWARDS PERSONALIZED MEDICINE: THE UTILITY OF PHARMACOGENOMIC TESTING TO SUPPORT THE TREATMENT OF BIPOLAR DISORDER



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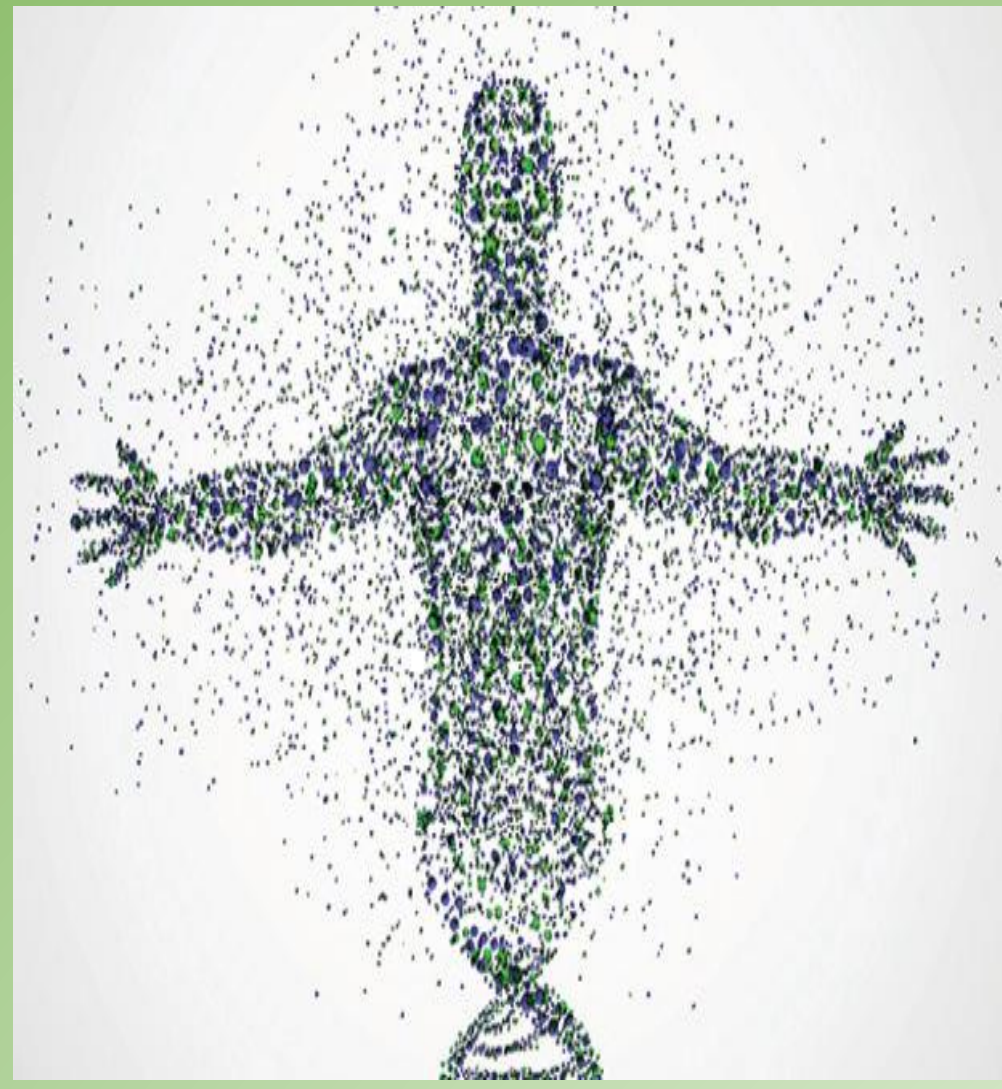
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## Background

Bipolar Disorder is a severe psychiatric illness, characterised by mood swings between mania and depression, with a life time prevalence in the order of 2.4% (Merikangas et al, 2011). It's a chronic disease, in which affective episodes may produce significant personal distress, social dysfunction and destructive effects on sufferers' psychological, professional and social welfare (Phillips & Kupfer, 2013; Gonzalez-Pinto et al, 2010). Although effective treatments already exist, variability in outcome leads to a large numbers of treatment failures, included misdiagnosis of the disorder followed by inadequate or inappropriate treatment (Nasrallah, 2015) and problems due to drug-resistant, rapid-cycling and cognitive decline despite drug therapy (Peedicayil, 2014). Interindividual variation in drug response depends on a number of factors, including diagnostic accuracy, drug-drug interactions, renal and hepatic function, medical and psychiatric comorbidity. In addition, genetically determined pharmacokinetic and pharmacodynamic variability can influence medication response (Mrazek DA, 2010). Pharmacogenetic testing (PGT) is proposed as a method to expedite the process of determining the most efficacious medicine with minimal side effects by recognizing individual variability in genetics as a key component of drug response (Knisely MR, 2014). Although The Human Genome Project (HGP) has predicted that by 2020 the pharmacogenomics approach for predicting drug responsiveness will be standard practice for quite a number of disorders and drugs (Collins et al, 2001), nowadays PGT are only occasionally used in clinical practice.

The aim of this preliminary study was to identify the percentage of patients receiving an optimal therapy and to observe, 1 month after the test' result, if the psychiatrists had modified the therapy basing on the test' result and if patients' psychopathology has been improved.



## Materials and Methods:

In this preliminary assessment we have report 2 cases of a 30 patients sample affected by Bipolar disorder I-II, recruited from the «Ospedale di Circolo e Fondazione Macchi, (Varese)» and from the «Ospedale San Carlo Borromeo, (Milano)», not responder to the current therapy (CGI>3) and exposed to Pharmacogenetic test «Neurofarmagen».

For the psychopathology's assessment we have used the following scales:

Clinical Global Impression (CGI): for the global condition; Young Mania Rating Scale (YMRS): to estimate the maniac symptoms; Hamilton Depression Rating Scale (HDRS): for the evaluation of depressive symptoms and the Dosage Records Rating Scale (DOTES) to evaluate the drug- response and the adverse events (AES) related to the therapy. We have done this evaluation at T0 (at the recruitment) and at T1 (1 month after the test's result).

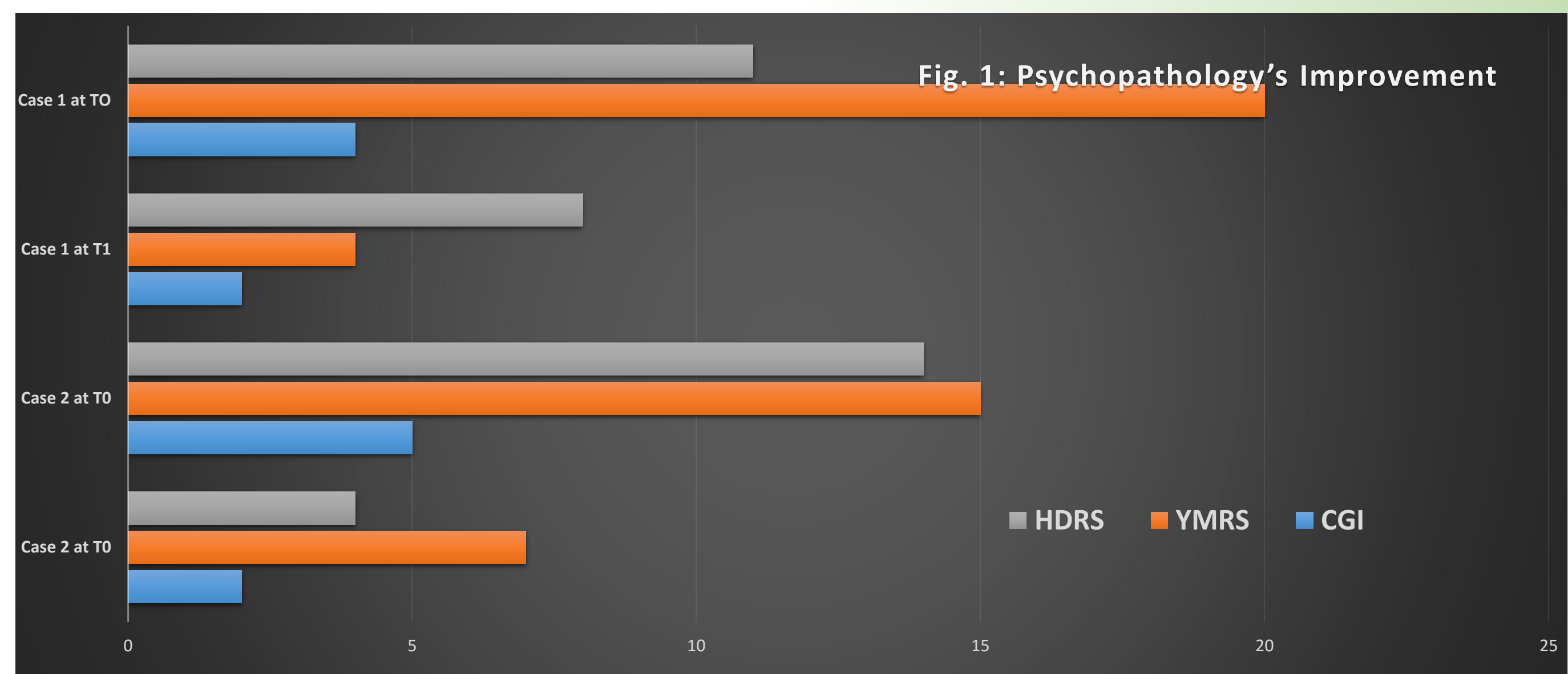
The study design was approved by the Ethics Committee.



## Results

Case 1: B.F., a 84 year-old male, diagnosed with Bipolar I Disorder, currently taking quetiapina and valproate. At T0 he was experiencing manic symptoms as shown by the psychometric tests: CGI=4, YMRS=20, HDRS=11 and he was referring hard constipation related to drugs. Genetic analysis revealed a CYP2D6 \*4/\*4 slow metabolizer, a CYP2C9 \*1/\*2 intermediate metabolizer and a CYP3A4 \*1/\*22 associated to an inadequate metabolize of quetiapina. At T1 the physician had modified the therapy following the test's indication: the test predicted a good response to lithium (CACNG2), so it was prescribed to the patient with an improving of the symptoms as shown by the decrease of the scales' scores reported in figure 1.

Case 2: S.P., a 36 year old male, diagnosed with Bipolar II Disorder, currently taking aripiprazole. At T0 he was experiencing a mix manic episode as shown by the psychometric tests: CGI= 5, YMRS= 14, HDRS= 15 without AES. Genetic analysis revealed a CYP1A2 \*1F/\*1F ultrarapid metabolizer, CYP2C9 \*1/\*2 intermediate metabolizer, associate with a standard response to aripiprazole and with a high risk of extrapyramidal symptoms. At T1, according to the test' s result, the psychiatrist had modified the therapy replacing aripiprazole with valproate. Also this second patient showed an improvement of the symptoms as shown by the decrease of the scales' scores reported in figure 1.



## Conclusions

The potential to tailor psychiatric medication choice and dose based on pharmacogenetic test results holds great promise for patients and providers to shorten the time between diagnosis and effective illness management (Thompson et al, 2015). There are many potential future roles for molecular genetics in the clinical management of psychiatric conditions (Bassett and Costain, 2012). In this preliminary study the PGT revealed that both patients were taking suboptimal therapies. In both patients the therapeutic regimen was modified following the test's result obtaining an improvement of the psychopathology. These preliminary data did not show only the utility of PGT for patients but also the positive psychiatrists' attitude towards genetic testing in psychiatric patient care.

This preliminary assesment encourage us to recruit the other patients, giving a significant contribution to the development of personalized medicine protocols.

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