heimer's disease and other dementias (assessed according to disability-adjusted life years measured for all ages) increased by an estimated 99.3% between 1990 and 2010,[1] and associated years lived with disability (YLDs) are on par with or exceed YLDs associated with diseases such as tuberculosis, the human immunodeficiency virus and the acquired immune deficiency syndrome, and malaria.[2] Key strategies for leveraging scarce resources to provide accessible and high-quality mental health services — including integration across care delivery platforms, collaborative care, and task sharing — hold equal promise for disorders that disproportionately affect the elderly. The problem is that few services for dementia care have been implemented in poor countries, and elder care in richer countries is still inadequate.

We endorse the argument made by Korboe and Carney that indigenous mental health care systems, which are currently marginalized and underused in mainstream practice, can be mobilized to benefit their communities. Over the past five decades, it has repeatedly been shown that tapping assets in the folk and popular sectors of care can expand the repertoire of therapeutics and hone the cultural fit of interventions. The limits and misuses of indigenous care also have been shown. Regrettably, advances in the implementation of traditional interventions have still been inadequate, but rigorous evaluation of the effectiveness of interventions aligns with priorities set out in the ambitious global research agenda for mental disorders.[3]

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Primaquine Failure and Cytochrome P-450 2D6 in *Plasmodium vivax* Malaria

TO THE EDITOR: Primaquine is the only medication approved by the Food and Drug Administration to eradicate the hypnozoites of *Plasmodium vivax*, but relapses of *P. vivax* malaria due to drug failure occur.[1] Human cytochrome P-450 isoenzyme 2D6 (CYP2D6) may be a key enzyme involved in metabolizing primaquine into redox-active metabolites against hypnozoites in the liver.[2,3]

As part of a phase 1 clinical trial of a vaccine against *P. vivax* (Study of VMP001 and AS01B in Healthy Malaria-Naive Adults; ClinicalTrials.gov number, NCT01157897), 33 participants were exposed to *P. vivax* sporozoites from the bites of infected mosquitoes. Parasitemia developed in all participants by day 13 after the challenge, and parasitemia rapidly cleared on initiation of the directly observed administration of a combination of chloroquine (at a dose of 1500 mg base by mouth over a period of 48 hours) and primaquine (at a dose of 30 mg by mouth daily for 14 days). Two participants (6%) had multiple relapses of malaria (see Fig. 1 in the Supplementary Appendix, available with the full text of this letter at NEJM.org). After each relapse, parasitemia was rapidly cleared in these participants with chloroquine (at a standard dose of 1500 mg base by mouth over a period of 48 hours) and a weight-based dose of primaquine (at a total dose of 6 mg per kilogram of body weight). To our knowledge, true resistance to primaquine in *P. vivax* hypnozoites has not been described; this suggests a role for host factors in drug failure.[1] We sought to identify an association between CYP2D6 activity and primaquine drug failure.

CYP2D6 phenotypes were ascertained in 25 available participants. The institutional review boards of the Walter Reed Army Institute of Research, the Naval Medical Research Center, and the Walter Reed Army Medical Center, as well as the Western Institutional Review Board approved the study, and all participants provided written informed consent. CYP2D6 phenotyping was performed; 21 participants had an extensive-

Table 1. Episodes of Malaria Relapse up to 20 Months after Challenge, According to CYP2D6 Activity Phenotype.

Metabolizer Phenotype*	AS–Model A Score	≥1 Relapse†	Total No. of Relapses‡
		no. of patients/total no. (%)	
Poor	0	1/1 (100)	3
Intermediate	0.5	1/3 (33)	2
Extensive	1	0/7	0
Extensive	1.5	0/8	0
Extensive	2	0/6	0

* CYP2D6 phenotypes were predicted with the use of the Activity Score (AS)–Model A tool to interpret the CYP2D6 genotype of each participant.[5] AS–Model A scores range from 0 to 2, with 0 indicating little or no CYP2D6 activity and 1 or 2 indicating normal levels of CYP2D6.[5] Participants with poor-metabolizer or intermediate-metabolizer phenotypes, which are consistent with reduced CYP2D6 production, were more likely to have primaquine failure.

† Participants with low AS–Model A scores, as compared with participants with higher scores, were more likely to have a malaria relapse (P=0.008, Cochran–Armitage trend test).

‡ A Poisson regression model showed a significant relationship between phenotypes that were consistent with low CYP2D6 production and more episodes of relapse over time (P=0.002).

metabolizer phenotype (at least one allele coding for an enzyme with normal activity) (84%), 3 participants had an intermediate-metabolizer phenotype (heterozygous for one null and one reduced-function allele) (12%), and 1 participant had a poor-metabolizer phenotype (two nonfunctional alleles) (4%)[4,5] (Table 1 in the Supplementary Appendix).

There were no relapses in the extensive-metabolizer group, two relapses in one participant in the intermediate-metabolizer group, and three relapses in the one participant in the poor-metabolizer group (Table 1). Although the sample size was small, there were significant associations between low-activity CYP2D6 phenotypes and the initial relapse and number of relapses up to 20 months after the challenge (Table 1). Plasma concentrations of the parent primaquine were measured in most of these participants for 24 hours after oral administration of 30 mg of primaquine. Participants with relapse had significantly decreased clearance of primaquine and the highest residual plasma concentrations after 24 hours (Fig. 2 and Table 2 in the Supplementary Appendix). This effect, which was consistent with decreased metabolism by CYP2D6, was most apparent in Participant 1 (who had the poor-metabolizer phenotype) and Participant 2 (who had the intermediate-metabolizer phenotype) (Fig. 2 in the Supplementary Appendix).

These data support our hypothesis that a primaquine metabolite responsible for hypnozoite killing is generated by a CYP2D6-dependent pathway. We propose that these persons have polymorphisms in CYP2D6 resulting in diminished metabolism of primaquine such that sufficient levels of the active metabolite were not achieved. These data suggest that host genetics may contribute to primaquine failure in persons who have relapse of *P. vivax* malaria. Larger study populations are necessary to further elucidate the relationships among CYP2D6 activity, geographic regional dosing requirements, and clinical failure of primaquine to eradicate *P. vivax* hypnozoites.

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