Tomoda suggests that specific subgroups of patients, including those with severe stenosis or heart failure, may benefit from stenting. In our study, we found no benefit in patients with severe stenoses (≥80% according to investigator evaluation) or with global ischemia, and we found no benefit in preventing hospital admissions for heart failure. Approximately 12 to 15% of the patients had heart failure at study entry. Some people, such as those with severe kidney disease or rapidly progressive renal failure, may not have been well represented in the study. Renal-artery stenting may benefit some of the patients described by Tomoda; however, data are lacking from randomized, controlled clinical trials to support that hypothesis. The results of our study suggest that most patients in stable condition should receive medical therapy regardless of the initial level of kidney function.

In reply to Leesar and colleagues: a type II error is possible, but the CORAL study was designed to achieve and did achieve adequate power to exclude a meaningful benefit with respect to the prevention of clinical events. Leesar et al. ask whether patients with a pressure gradient across the renal-artery stenosis might benefit from renal-artery stenting, as is suggested in several studies that used a surrogate end point, systolic blood pressure, as the outcome. In our study, we found a small but significant reduction in systolic blood pressure of 2 mm Hg favoring stent treatment; this reduction did not translate into a benefit with respect to event-free survival. In our study, we did obtain data on translesional renal-artery pressure gradients, and analyses of these data should be informative about the value of determinations of pressure gradients.

With regard to the letter by Mahé and Jaquinandi: we considered the renal resistance index as a variable that might be predictive of treatment outcomes, and we prospectively included that measure in an analysis involving the ultrasonographic findings in a subgroup population. However, the renal resistance index has not been proved conclusively to be useful in selecting patients for renal-artery revascularization.[1-3]

Zanoli and colleagues report that smaller renal arteries (<5.2 mm) and smaller renal-artery lumen diameters (<2.9 mm) are associated with lower glomerular filtration, resistant hypertension, and a higher risk of cardiovascular events among people undergoing coronary angiography. Data are lacking from observational studies to replicate this relationship. If we assume that this relationship will be replicated in future observational studies, the conclusion of our study remains that medical therapy appears to work as well as stenting with medical therapy in patients with renal-artery stenosis.

Timothy P. Murphy, M.D.
Lance D. Dworkin, M.D.
Rhode Island Hospital
Providence, RI

Christopher J. Cooper, M.D.
University of Toledo
Toledo, OH
christopher.cooper@utoledo.edu

Since publication of their article, the authors report no further potential conflict of interest.

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Variant *GADL1* and Response to Lithium in Bipolar I Disorder

TO THE EDITOR: Chen et al. (Jan. 9 issue)[1] report a dramatic association between the response to lithium therapy and the presence of intronic single-nucleotide polymorphisms (SNPs) mapped to *GADL1*, suggesting a link to GADL1 function in the brain. However, a review of multiple databases of adult brain expression (both microarray and RNA sequencing) reveals that GADL1 shows at most very low expression across diverse brain regions.[2,3] Furthermore, we have observed minimal if any GADL1 expression in 600 brains obtained on autopsy, including those from patients with bipolar disorder (in samples from the Lieber Institute for Brain Development) that were ana-

lyzed by means of RNA sequencing with deep coverage (average, 50 million 100-bp paired-end reads, with 100 million reads per sample). This finding is especially puzzling, given the strong clinical association. An alternative possible mechanism for the pharmacogenetic association involves the kidney, in which GADL1 appears to be more abundantly expressed. Despite its name, there is no evidence that GADL1 is GAD-like in brain function. Rather, a physiologic role for GADL1 in taurine biosynthesis has been suggested, with potential relevance to kidney function.[4,5] We therefore encourage a retrospective review of kidney function and lithium levels in patients, stratified according to *GADL1* genotype, in the study by Chen et al.

Rebecca Birnbaum, M.D.

Johns Hopkins Hospital
Baltimore, MD

Joo Heon Shin, Ph.D.
Daniel Weinberger, M.D.

Lieber Institute for Brain Development
Baltimore, MD
drweinberger@libd.org

No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: With regard to the article by Chen et al.: we calculated the odds ratio for each genotype to emphasize the strength of the associations in the combined cohorts. Thus, as compared with patients who were homozygous for the C allele, those who were heterozygous for the T allele had an odds ratio of 73.5 (95% confidence interval [CI], 35.3 to 153.3), whereas for those who were homozygous for the effective allele, the odds ratio rose to 228.7 (95% CI, 60.9 to 859.5; $P=1.7\times10^{-49}$ for trend).

Given the huge magnitude of the association between the presence of the T allele and the response to lithium therapy, we would like to ask the authors whether there was a significant difference in the minimum efficacious serum lithium level[1] between carriers and noncarriers of the "response" allele.

Nikolaos Vlachadis, M.D., M.P.H.
Nikolaos Vrachnis, M.D., Ph.D.
Emmanouel Economou, Pharm.D., Ph.D.

National and Kapodistrian University of Athens
Athens, Greece
vlaxadis@gmail.com

No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: We assessed 154 Japanese patients with bipolar disorder (109 patients with bipolar I disorder and 45 with bipolar II disorder) whom we evaluated using the Alda scale (with a score of 6 to 10 indicating a good response to lithium therapy and a score of 0 to 5 indicating a poor response).[1] We genotyped rs17026688 in *GADL1*, one of the two SNPs that showed the strongest associations with a response to lithium therapy in the genomewide association study by Chen et al. This SNP showed a large effect size (odds ratio, approximately 80). As a phenotypic definition, Chen et al. examined only patients with bipolar I disorder and those with an Alda score of 0 on the first four items in criterion B. (On the Alda scale, criterion B, which is used to determine whether there is a causal relationship between clinical improvement and lithium therapy, is divided into levels B1 through B5, with each part scored as 0, 1, or 2 points.) However, as a relaxed phenotyping, we analyzed all patients with bipolar I disorder and bipolar II disorder who had an Alda score of 1 or less on items B1 through B4. We did not observe an association for any criterion (Table 1), even in the stringent phenotype analysis, as reported by Chen et al. This replication analysis did not support an association between *GADL1* variants and a response to lithium therapy in a Japanese population. Therefore, this variant is not an ideal predictor of

Table 1. Replication Analysis for the Association between rs17026688 and a Response to Lithium Therapy in 154 Japanese Patients.

Variable	Alda Score on Criteria B1–B4			
	Bipolar I Disorder		Bipolar I and II Disorder	
	0 (N=63)	≤1 (N=109)	0 (N=73)	≤1 (N=154)
Good response — no. of patients				
All genotypes*	26	38	30	52
TT	1	1	1	1
CT	9	14	10	18
CC	16	23	19	33
Poor response — no. of patients				
All genotypes*	37	71	43	102
TT	3	5	3	6
CT	12	21	13	34
CC	22	45	27	62
P value†				
For trend	0.69	0.90	0.77	0.50
Fisher's exact test	1.00	0.84	1.00	0.86
Odds ratio (95% CI)‡	0.92 (0.33–2.56)	1.13 (0.50–2.54)	0.98 (0.37–2.57)	0.89 (0.45–1.80)
Statistical power — %§				
Odds ratio, 80	100	100	100	100
Odds ratio, 10	97.1	99.9	98.8	100

* In 96 samples obtained from the patients in our analysis, we confirmed the finding of Chen et al. that a 1-base deletion in intron 8 of *GADL1* (IVS8+48delG) and rs17026688 were in absolute linkage disequilibrium ($r^2=1$).
† P values for trend are for the association between rs17026688 and the response to lithium. P values that were calculated with the use of Fisher's exact test are for the association between the presence of the T allele and the response to lithium (TT plus CT vs. CC).
‡ Odds ratios were calculated on the basis of the dominant model (TT plus CT vs. CC).
§ The statistical power was calculated by means of Fisher's exact test under the dominant model on the assumption of an allele frequency of 38% and a type I error rate of 0.05.[2]

the efficacy of lithium therapy among patients of Japanese ancestry.

Masashi Ikeda, M.D., Ph.D.
Kenji Kondo, M.D., Ph.D.
Nakao Iwata, M.D., Ph.D.
Fujita Health University School of Medicine
Aichi, Japan
nakao@fujita-hu.ac.jp

No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: The identification of robust biomarkers of medication response is key to precision medicine and offers the potential to improve treatment outcomes, especially in psychiatry.[1] The claim by Chen and colleagues that the response of patients with bipolar I disorder to lithium therapy is strongly associated with genetic markers in *GADL1* prompted us to undertake a replication study in 218 samples from patients collected by the Consortium on Lithium Genetics.[2] The alleles reported by Chen et al. are common in Asians but rare in whites, so we studied only the Asian samples obtained from the consortium. We tested 218 samples obtained from patients of Han Chinese or Japanese ancestry by

Table 1. Association between *GADL1* SNP rs17026688 and the Response to Lithium Therapy in Samples Obtained from 218 Patients of Asian Ancestry.*

Origin of Sample and Alda Score†	No. of Patients with No Response: No. of Patients with Response	Frequency of T Allele		Odds Ratio (95% CI)‡	P Value	
		No Response	Response		Trend	Fisher's Exact Test
		%				
Japan						
>5	88:39	23.3	15.4	0.52 (0.23–1.21)	0.18	0.18
>6	97:30	22.2	16.7	0.59 (0.24–1.46)	0.39	0.47
>7	102:25	22.1	16.0	0.51 (0.19–1.39)	0.37	0.44
Taiwan						
>5	72:19	30.0	23.7	0.58 (0.21–1.61)	0.40	0.55
>6	78:13	30.9	15.4	0.34 (0.10–1.21)	0.07	0.16
>7	80:11	30.8	13.6	0.29 (0.07–1.18)	0.07	0.13
Meta-analysis§						
>5	160:58	NA	NA	0.54 (0.28–1.04)	0.11	0.15
>6	175:43	NA	NA	0.49 (0.23–1.02)	0.08	0.16
>7	182:36	NA	NA	0.42 (0.19–0.95)	0.07	0.13

* All samples were obtained from the Consortium on Lithium Genetics. NA denotes not applicable.
† Three thresholds for response were tested on the Alda scale. For each item, patients whose total score exceeded the threshold were considered to have a good response; the rest of the patients were considered to have a poor response.
‡ Odds ratios are for the association between the T allele of the SNP (dominant model) and a response to lithium therapy. The SNP rs17026688 was imputed with the use of the MACH program (r^2>0.9).[4] All genotype distributions are consistent with Hardy–Weinberg equilibrium. Subsequent direct genotyping with the use of Taqman probes produced no discrepant genotypes.
§ In the meta-analysis, odds ratios and P values were estimated by means of a fixed-effects model. We also tested the association between the response to lithium therapy and another SNP (rs17026651) that was identified by Chen et al. as being significant, and the results were very similar as those shown here (data not shown). The frequency of the T allele was not calculated in the meta-analysis, since allele frequencies differed among samples owing to population differences.

means of genotyping on Illumina Omni 2.5M or OmniExpress arrays and evaluated the patients using the same Alda scale[3] that was used by Chen et al. The statistical power exceeded 99% at the lower end of all 95% confidence intervals reported by the authors.

We found no association between the variants and a response to lithium therapy at any threshold on the Alda scale (Table 1). Oddly, the two most significant markers in the study by Chen et al. trended in the opposite direction in our samples. Although small effects cannot be ruled out, we can find no support for the existence of a major gene affecting the response to lithium therapy among Asian patients.

The Consortium on Lithium Genetics

The members of the writing committee of the Consortium on Lithium Genetics (Liping Hou, Ph.D., Urs Heilbronner, Ph.D., Marcella Rietschel, M.D., Tadafumi Kato, M.D., Ph.D., Po-Hsiu Kuo, Ph.D., Francis J. McMahon, M.D., and Thomas G. Schulze, M.D.) take responsibility for the content of this letter.

Members of the Consortium on Lithium Genetics are listed in the Supplementary Appendix, available with the full text of this letter at NEJM.org.

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No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: Chen et al. describe an association between SNPs in a gene associated with the glutamatergic system and the response to lithium therapy. We would suggest that two points need some clarification. First, it is surprising that rapid cycling was found to be a positive predictor of a response to lithium therapy in these patients. This is not in line with previous studies and clinical experience.[1] Could this finding be related to the response criteria chosen for this trial, with a higher number of previous episodes being associated with a higher total score? Second, nonadherence to lithium therapy was not explained. One could assume that a lack of efficacy led to premature termination of therapy. We would recommend that the genetic analysis be extended to include patients who terminated therapy.

Ion Anghelescu, M.D.

Clinic Dr. Fontheim
Liebenburg, Germany

Michael Dettling, M.D.

Charité
Berlin, Germany

No potential conflict of interest relevant to this letter was reported.

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DOI: 10.1056/NEJMc1401817

THE AUTHORS REPLY: Birnbaum et al. argue that there is no evidence that GADL1 is GAD-like in brain function, and that GADL1 may be involved in taurine biosynthesis related to renal function. They mention that a physiologic role for GADL1 in taurine biosynthesis has been suggested. The physiologic function of GADL1 in the human brain still needs to be elucidated. Taurine may cross the blood–brain barrier and has been implicated in several physiologic phenomena, such as interacting directly with the glutamate NMDA receptor.[1]

We thank Vlachadis et al. for bringing to our attention an error in Table 2 of our article, which we have corrected. (The odds ratio for the association between the presence of the T allele and a response to lithium therapy in the combined cohorts should be 88.5 [95% confidence interval, 41.4 to 198.0].) Regarding their query about any difference in the minimum efficacious serum level of lithium between carriers and noncarriers among patients with a good response to lithium therapy, we were not able to examine this issue in our retrospective study. The prescribed lithium doses and the time of the day that blood was drawn for assessing lithium levels were not fixed during the period when the majority of the 394 study patients were taking lithium, which led to varied blood levels of lithium. We can only identify patients whose reported lithium levels were equal to or exceeded 0.5 mmol per liter.

Both Ikeda et al. and Hou et al. cannot replicate our findings in their Japanese and Han Chinese samples. On the basis of their comments, we trust that the two groups have not duplicated the methods that we used in the phenotype definition and assessment, as described in detail in our article and in its online Supplementary Appendix. We are willing to provide help with independent replication studies.

Anghelescu and Dettling criticize our finding of a better response to lithium therapy among patients with rapid cycling. The relationship between rapid cycling and the effect of lithium is still controversial.[2] The adherence to lithium maintenance treatment involves factors related to patients (illness behavior and cognitive function), psychiatrists (rapport with patients), treatment (any serious adverse effects), and social environment (familial and financial supports). One cannot assess the effect of lithium in patients with premature termination because of any of the above factors.

Chau-Shoun Lee, M.D., Ph.D.
Mackay Memorial Hospital
Taipei, Taiwan

Andrew Tai-Ann Cheng, M.D., Ph.D., D.Sc.
Academia Sinica
Taipei, Taiwan
bmandrew@gate.sinica.edu.tw

Since publication of their article, the authors report no further potential conflict of interest.

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Prevention of Preterm Parturition

TO THE EDITOR: In discussing prevention of preterm birth, Iams (Jan. 16 issue)[1] correctly identifies smoking as a major risk factor. However, the prevention of exposure to secondhand smoke during pregnancy also is an opportunity to prevent preterm birth. The Surgeon General's 2006 report on involuntary tobacco smoke exposure showed that the relationship between secondhand smoke and preterm delivery was "suggestive" of causation.[2] However, since then, further data have been published. These include the results of two studies that strengthen the evidence for the association between preterm birth and secondhand-smoke exposure, with odds ratios of 2.30 (95% confidence interval [CI], 0.96 to 5.96)[3] and 1.61 (95% CI, 1.30 to 1.99),[4] along with studies showing a reduction in the rate of preterm births after the adoption of smoke-free workplace laws.[5]

In consideration of this evidence linking secondhand-smoke exposure and preterm birth and the biologic plausibility, clinicians should ask about and counsel methods for eliminating such exposure to minimize the risk of preterm birth. Clinical actions might include treatment for tobacco dependence for all household members, maternal avoidance of secondhand smoke, and strict smoke-free policies.

Jonathan P. Winickoff, M.D., M.P.H.
MassGeneral Hospital for Children
Boston, MA
jwinickoff@mgh.harvard.edu

Jonathan D. Klein, M.D., M.P.H.
American Academy of Pediatrics Julius B. Richmond Center
Elk Grove Village, IL

No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: We were surprised that the article by Iams did not discuss the pessary as a treatment option for preterm birth. Trials have suggested that it is effective in both twin and singleton pregnancies.[1,2]

In women with a singleton pregnancy and a short cervix, the Pesario Cervical para Evitar Prematuridad (PECEP) trial[2] showed that pessary use was associated with a significant reduction in the risk of preterm birth before 34 weeks of gestation (odds ratio, 0.18; 95% CI, 0.08 to 0.37), which was the primary outcome; the study also showed a significant reduction in a composite measure of adverse neonatal outcomes (odds ratio, 0.14; 95% CI, 0.04 to 0.39). In women with a multiple pregnancy and a short cervix, the Pessaries in Multiple Pregnancy as a Prevention of Preterm Birth (ProTWIN) trial showed a similar reduction in adverse neonatal outcomes (risk ratio,