**Annals of Internal Medicine**

**COMMENTS AND RESPONSES**

**Ampicillin plus Ceftriaxone for High-Level Aminoglycoside-Resistant Enterococcus faecalis Endocarditis**

**TO THE EDITOR:** The antimicrobial synergism of ampicillin plus ceftriaxone to treat high-level aminoglycoside-resistant (HLAR) Enterococcus faecalis endocarditis, as shown by Gavalda and colleagues (1), is important. However, certain basic questions need to be answered before this treatment can be incorporated into everyday practice. First, enterococci are inherently resistant to cephalosporins, including ceftriaxone. Second, ampicillin and ceftriaxone are both β-lactam antibiotics with a common mechanism of action: inhibition of synthesis of the bacterial peptidoglycan cell wall. Antimicrobial agents acting on different targets may enhance the overall antimicrobial activity. How then can there be synergy between these 2 drugs? Treatment of HLAR E. faecalis depends on precise determination of antibiotic susceptibilities, testing for bactericidal activity, ascertaining of the serum inhibitory and bactericidal titers, and monitoring of drug concentrations in the serum. Although aminoglycoside resistance is often present, these drugs can still synergize with cell-wall inhibitors, provided that the aminoglycoside’s minimal inhibitory concentration is 1000 mg/L or less (2). Streptomycin is with cell-wall inhibitors, provided that the aminoglycoside’s minimal inhibitory concentration is often present, these drugs can still synergize. Monitoring of drug concentrations in the serum. Although aminoglycoside resistance is often present, these drugs can still synergize with cell-wall inhibitors, provided that the aminoglycoside’s minimal inhibitory concentration is often present, these drugs can still synergize with cell-wall inhibitors, provided that the aminoglycoside’s minimal inhibitory concentration is often present, these drugs can still synergize. Monitoring of drug concentrations in the serum. Although aminoglycoside resistance is often present, these drugs can still synergize with cell-wall inhibitors, provided that the aminoglycoside’s minimal inhibitory concentration is often present, these drugs can still synergize.

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**Potential Financial Conflicts of Interest:** None disclosed.

**References**

**IN RESPONSE:** We read with interest the letter by Dr. Singh regarding our article. First, we would like to clarify that the cure rate for HLAR E. faecalis endocarditis was 71.4%, far greater than the best cure rate reached with a cell-wall–susceptible agent alone or in combination with other therapy. After careful review of our article, we found no figure or data that could lead to this confusion. Second, Dr. Singh’s question about the synergic effect of ampicillin plus ceftriaxone was evaluated in vitro by Mainardi and colleagues (1) and by our group in different studies in the experimental endocarditis model (2, 3). Mainardi and colleagues (1) used amoxicillin and cefotaxime and proposed that, at low amoxicillin concentrations, the low-molecular-weight penicillin-binding proteins (PBPs) 4 and 5 would be partially saturated, but the nonessential PBPs 2 and 3 could participate in building the cell wall. The combination with cefotaxime would totally saturate PBPs 2 and 3, producing the bactericidal synergistic effect. Thereafter, our group showed that the combination of ampicillin plus ceftriaxone was as effective as ampicillin plus gentamicin for the treatment of experimental endocarditis due to non-HLAR Enterococcus faecalis (2) and more effective than ampicillin alone in experimental endocarditis due to HLAR Enterococcus faecalis (3). Third, although we agree with Dr. Singh about the possible usefulness of the combination of ampicillin plus gentamicin if the aminoglycoside’s mean inhibitory concentration is between 500 and 1000 mg/L, this may be only theoretical. Judging by the results of our study, the combination of ampicillin plus ceftriaxone would be more successful.

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**Potential Financial Conflicts of Interest:** None disclosed.

**References**

**Pitfalls in Linking Cost Sharing to Value**

**TO THE EDITOR:** Braithwaite and Rosen (1) present an intriguing argument for enhancing patient adherence to “high-value” medical therapies, namely removal (or reduction) of cost-share obligations by the third party bearing risk. The authors correctly identify a major barrier to implementing their proposal—actuarial amortization of the added cost to the payer, when the “payback” (medical offset) from reduction in service utilization may occur with an uncertain time horizon, if at all.

Payers in North America, Europe, and Australia have attempted a value-based copayment system within their prescription drug benefit in recent years, known as “reference-based pricing.” In this system, the lowest copayment tiers are assigned to drugs with the highest cost-effectiveness, incorporating net acquisition price (including

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rebates and discounts), time to illness remission, relative efficacy, potency, patient adherence factors, and therapeutic index (2). The system, unfortunately, is limited to the few drug classes for which abundant head-to-head studies are available, including reliable comparisons of the above variables. Few of the studies satisfy stringent cost-effectiveness analytic criteria. To cite a political problem, clinical staff employed by payers and charged with the obligation to recommend those treatments for copayment reductions may be accused of caprice, conflict of interest, and lack of sensitivity to clinical practice guidelines and subspecialty-driven parochial priorities.

I take issue with the authors’ choice of words that pharmaceutical copayments “penalize” patients. A benefit that obligates the payer for 65% to 80% of the ingredient cost of the drug (3) should not be thought of as punitive to the member, although the authors cite evidence that moving toward 100% payer obligation enhances beneficiary adherence. A possible starting point for copayment reduction would be to use adjudicated treatment goals, promulgated by external organizations with quality benchmarks (that is, Healthcare Effectiveness Data and Information Set [HEDIS] measures), and to bring all payers together within a given marketplace to agree on the same degree of copayment relief. In this way, the most generous payer, who might otherwise act unilaterally, is not subject to adverse beneficiary selection—a very real concern for insurers. Furthermore, all payers would be underwriting equally the future windfall of healthier patients who change plans and exhibit utilization reduction only after plan conversion.

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Potential Financial Conflicts of Interest: None disclosed.

References

IN RESPONSE: We thank Dr. Polsky for highlighting several substantive issues. Reference pricing (that is, paying the price of only the cheapest drug within a class of similarly effective drugs) is only 1 among many ways to link cost sharing to value, and it also only concerns drugs within a particular class. We endorse an approach that is sufficiently flexible to address a broad range of drug and nondrug clinical alternatives.

We recognize that cost-sharing decisions may be plagued by accusations of caprice and conflict of interest, and these same concerns motivated our work. We have proposed a more objective method of making cost-sharing decisions that may ultimately diffuse some of this criticism. A new national center for comparative clinical effectiveness research may further enhance these efforts.

Evidence limitations are always an important concern in medical decision making. However, endorsing a particular decision-making framework may lead to greater efforts to gather relevant evidence. New approaches may make the use of existing evidence more transparent (1). “Abundant, head-to-head studies” may not always be necessary, particularly if additional data would be unlikely to change a decision (2).

Waiving cost-sharing for HEDIS measures is a sensible idea that is complementary rather than alternative to our approach. However, only some high-value interventions may be encompassed by HEDIS measures. Conversely, some HEDIS measures may lack evidence of cost-effectiveness. We advocate using a more conceptually robust and generalizable method.

We agree with Dr. Polsky that pharmaceutical copayments should, in general, not be considered penalties. However, when there is overwhelming evidence of cost-effectiveness, copayments may act as such. Indeed, in the rare circumstances when therapies are cost-saving (for example, β-blockers after myocardial infarction), a logical extension of the cost-sharing ethos would be to share that cost savings with the patient (that is, to provide a small inducement for adherence).

Finally, Dr. Polsky raises 2 common concerns for payers: Can value-sensitive health plans be implemented in practice, and will they save money? These questions have different answers. Pitney Bowes, University of Michigan, Marriott, and Mohawk Industries are just a few examples of employers that have successfully adopted value-based copayment programs, so they are definitely feasible. However, it is not appropriate to expect that these programs will always save money. We must remember that the primary return on a health care spending investment is good health.

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Potential Financial Conflicts of Interest: None disclosed.

References

The Effect of a Primary Care Practice-Based Depression Intervention on Mortality in Older Adults

TO THE EDITOR: Gallo and colleagues (1) recently reported that a depression care management intervention significantly reduced risk for 5-year mortality among older primary care patients who have major depression compared with patients receiving usual care. No deaths from suicide among patients with major depression occurred in either group. The results from this study are of potentially great importance. Despite many studies that report prospective relationships between depression and important outcomes, such as mortality,
Little evidence suggests that depression treatment reduces overall mortality rates.

The statistical methods that Gallo and colleagues used for covariate adjustment, however, are known to result in model overfitting, which raises the question of whether these findings would generalize to other similar patient samples. On an unadjusted basis, patients in the intervention practices with major depression were not at lower risk for mortality. They were at significantly lower risk only after adjustment for 10 “influential covariates” that Gallo and colleagues identified on the basis of significant univariate associations with time to death. Methods like this, however, which prescreen variables for subsequent entry into multivariate regression analyses, are indirect versions of automated variable selection procedures (for example, stepwise regression) (2). The statistical guidelines published online by Annals of Internal Medicine (3) counsel against prescreening variables and state that “[a]uthors should avoid stepwise methods of model building, except for the narrow application of hypothesis generation for subsequent studies.” It has been amply demonstrated that prescreening and other automated variable selection methods capitalize on variability unique to a given sample, radically underestimate the degrees of freedom used to determine estimates in regression models, often generate substantially inflated type I error rates and artifically small P values, and do not consistently produce replicable findings (4).

In Gallo and colleagues’ study, the combined effect of adding the group of 10 preselected “influential covariates” was to substantially elevate, and possibly exaggerate, the hazard ratio associated with the intervention for patients with major depression. It also produced the surprising finding that these results were largely due to a reduction in deaths related to cancer (15 in usual care practices vs. 8 in treatment practices). Gallo and colleagues concluded that further investigation is needed to clarify the mechanisms behind the relationship between the depression intervention and decreased mortality risk from cancer. Given the limitations of their analytical methods, however, investigation of causal mechanisms is not warranted until the basic findings of the study are reproduced.

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References

IN RESPONSE: We appreciate Drs. Thombs and Ziegelstein’s observation that our study was of great importance in reporting the beneficial effect of a depression intervention on mortality. Drs. Thombs and Ziegelstein were concerned that the post hoc selection of covariates for inclusion only if they were associated with the outcome led to overfitting and ignored the issue of confounding. We had a prespecified approach to identifying and including potential confounders because we knew that imbalances would be likely and that adjustment with patient-level variables would be necessary given the practice-randomized design. Our prespecified approach did address the concern about confounding by identifying potential confounders for inclusion in the model by their association (P = 0.100) with the interaction variables of interest, randomization assignment, and baseline depression status, as well as the dependent variable, time to death. Using this approach, only age, level of educational attainment, baseline smoking status, history of myocardial infarction reported at baseline, and baseline suicidal ideation were identified as potential confounders. The intention-to-treat hazard ratio and corresponding 95% CI for patients with major depression was consistent with the reported result (adjusted hazard ratio, 0.62 [CI, 0.42 to 0.92]). Additional variables for which we adjusted the point estimates reported in Table 4 were requested by reviewers. We want to emphasize the prespecified nature of our statistical approach and the care with which we selected variables for inclusion in models. The surprising finding relating to a reduction in cancer deaths was unadjusted and therefore was not influenced by the selection of covariates in multivariate models. We stated that any “evidence of a potential association of practice intervention assignment and specific causes of death must be viewed as an opportunity for generation of hypotheses to be tested in future intervention research.” We did not call for research on mechanisms related to the decreased mortality risk from cancer. On the other hand, we would not want to be dismissive of the findings with regard to cancer deaths. We did suggest that mediators of the effect of a depression intervention on mortality deserve further study to increase our understanding of how depression leads to increased mortality. We believe this is the first publication of a randomized clinical trial to report decreased mortality in association with treatment of depression. Replication would be welcome.

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Repair of Unruptured Abdominal Aortic Aneurysm

TO THE EDITOR: In a systematic review of repair of unruptured abdominal aortic aneurysm (AAA) by Lederle and colleagues (1), endovascular repair did not reduce all-cause mortality (relative risk, 0.95 [95% CI, 0.76 to 1.19]) but did reduce AAA-related midterm mortality (relative risk, 0.53 [CI, 0.31 to 0.92]) compared with open
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repair. However, the results of the EVAR (Endovascular Aneurysm Repair) I trial, 1 of the 3 trials included in the systematic review, were recently updated: The number of patients enrolled increased from 1082 to 1252 patients, and the follow-up was extended from median of 2.9 years to mean of 3.8 years (2). Therefore, we performed a meta-analysis of currently available results of randomized, controlled trials of endovascular versus open repair of AAA, including the updated results of the EVAR I trial. 2.

Our comprehensive search identified 3 randomized trials that have published midterm follow-up results: the DREAM (Dutch Randomized Endovascular Aneurysm Management) trial (3); the EVAR I trial (2); and a trial from Montréal, Québec, Canada (4). Of these 3 individual trials, 2 demonstrated a statistically nonsignificant benefit of endovascular over open repair for AAA-related midterm mortality (relative risk, 0.27 [CI, 0.06 to 1.19] in the DREAM trial and 0.61 [CI, 0.36 to 1.03] in the EVAR I trial), but only the Montréal trial demonstrated a statistically nonsignificant benefit of open over endovascular repair (relative risk, 3.00 [CI, 0.13 to 69.52]). Pooled analysis of the 3 trials demonstrated a statistically nonsignificant reduction in AAA-related midterm mortality with endovascular versus open repair in a random-effects model (relative risk, 0.57 [CI, 0.32 to 1.02]). We found neither between-study heterogeneity of results, analyzed by using standard chi-square tests ($P = 0.35$), nor evidence of significant publication bias, assessed by using an adjusted rank-correlation test ($P = 0.60$). Pooled analysis also demonstrated a statistically nonsignificant reduction in all-cause midterm mortality with endovascular versus open repair (relative risk, 0.98 [CI, 0.81 to 1.18]).

Despite the results of Lederle and colleagues’ systematic review (1), our meta-analysis of all currently available results of randomized, controlled trials failed to demonstrate significant benefit of endovascular over open repair for not only all-cause but also AAA-related midterm mortality.

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References

Clinical Observation

Translation of Genetic Discoveries into Clinical Therapies

Background: Discovering the genetic basis for human disease is thought to be a key step in the search for new treatments.

Objective: To examine the rate at which genetic discoveries translate into randomized trials and approved treatment options, focusing on highly cited genetic research, because such visible work is generally more likely to be tested in the clinical domain (1, 2).

Methods: To identify genetic discoveries, we used Web of Science to search all genetic, medical, and biological journals that publish genetic research and have a citation impact factor of 5 or greater (3). We included original reports of genetic determinants for human diseases that were published between 1975 and 2000 and cited at least 1000 times. We supplemented this search by scanning for references in the Online Mendelian Inheritance in Man database and hand searching Annual Review of Genetics and personal files. Sample size calculations ($\alpha = 0.05; \beta = 0.05$) estimated that 49 articles were needed to exclude a translation rate of less than 5%. Appendix Table 1 and the Appendix Figure (both available at www.annals.org) summarize the keywords used and journal searched and the study flow.

For each genetic discovery, we performed a subsequent search for randomized trials in 11 sources: ACP Journal Club, Allied and Complementary Medicine Database, BIOSIS Previews, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Database of Abstracts of Reviews of Effects, EMBASE, International Pharmaceutical Abstracts Database, MEDLINE, the National Institutes of Health Clinical Trials Database, and Web of Science (all from inception to 1 March 2007). In addition, for each gene, 2 experts were contacted to inquire about additional trials. We considered translation to trials to have occurred if a randomized trial of efficacy for a treatment modulating the gene, gene product, or immediate downstream pathway was statistically positive according to primary outcome. To examine translation to approved treatments, we searched regulatory databases in the United States, Canada, United Kingdom, and Europe.

Results: From an initial list of 605 highly cited candidate publications, we found 53 that identified genetic determinants for human diseases (Appendix Table 2, available at www.annals.org). The included reports were cited a median of 1316 times (range, 1005 to 4831 times). The median follow-up interval for potential translation was 14 years (range, 9 to 16 years).

We found randomized trials for 20 of the 53 genetic discoveries; 15 of these were positive and 5 were not. The rate of translation to randomized trials was therefore 28% (95% CI, 18% to 42%). Eight of the genetic discoveries have translated to approved treatment options (15% [CI, 8% to 27%]). Journal; year of publication; number of times the work was cited; type of disease; and the location, function, and properties of the gene product did not predict translation in univariable or multivariable logistic regression analysis.

Discussion: A possible dividend of genetic research is the development of therapies for human disease. We found that about a quarter of landmark genetic discoveries resulted in positive randomized, controlled trials and in 7 resulted in approved treatment options over a median follow-up of 14 years. A limitation of these
data is our focus on highly cited research; less visible work might yield lower rates of translation.

These data may have implications for the development of new therapies. Given that more than 92% of investigational agents entering phase I trials fail to achieve regulatory approval, analyzing genetic discoveries for new treatment approaches may be more fruitful (4). Our finding that nearly two thirds of such discoveries have not yet been tested in randomized trials suggests much untapped potential. Finally, by quantifying the rate of translation to clinical therapies, these data lend some support for the strategy of uncovering the genetic basis for human disease.

Conclusion: Landmark genetic discoveries yield positive randomized, controlled trials and approved treatments frequently enough to justify investments into genetic research.

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Potential Financial Conflicts of Interest: None disclosed.

References

CORRECTIONS

Correction: Diagnosis and Treatment of Low Back Pain

The recent joint guideline by the American College of Physicians and the American Pain Society on diagnosis and treatment of low back pain (1) and supporting evidence reviews (2, 3) contained several errors. In the original print version of the guideline, the target populations were described incorrectly (1). The word not was inadvertently dropped from a sentence that described populations that were excluded from the guideline. Children or adolescents with low back pain; pregnant women; and patients with low back pain from sources outside the back (nonspinal low back pain), fibromyalgia or other myofascial pain syndromes, and thoracic or cervical back pain are not covered by the guideline.

In response to an online letter to the editor (4), we re-reviewed the evidence on acetaminophen and believe we originally graded the evidence too positively in the guideline and evidence review (1, 2). However, our guideline recommendations remain the same. Acetaminophen for acute low back pain should be rated fair rather than good quality. Acetaminophen for chronic low back pain should be rated fair rather than good quality, and magnitude of benefit should be small rather than moderate. (Appendix Table 5 and Appendix Table 6 in the guideline [1] and Appendix Table 10 and Appendix Table 11 in the evidence review [2] have been corrected.) The Data Synthesis section in the abstract of the evidence review (2) should have read: “We found good evidence that NSAIDs [nonsteroidal anti-inflammatory drugs], skeletal muscle relaxants (for acute low back pain), and tricyclic antidepressants (for chronic low back pain) are effective for pain relief... We also found fair evidence that acetaminophen, opioids, tramadol, benzodiazepines, and gabapentin (for radiculopathy) are effective for pain relief.” The Conclusions section of the abstract should have read: “Medications with good evidence of short-term effectiveness for low back pain are NSAIDs, skeletal muscle relaxants (for acute low back pain), and tricyclic antidepressants (for chronic low back pain).” Similar changes should be applied to the Discussion section. As noted, these changes do not affect Recommendation 6, which suggests acetaminophen as an option for first-line pharmacologic therapy (1). This recommendation is based largely on the safety profile of acetaminophen, when taken in appropriate dosages in patients without a contraindication.

Reference 62 in the evidence review on medications for low back pain is incorrect and should refer to a different trial by the same first author (5).

In the evidence review on medications, we inverted (calculated 1/relative risk) results for “not achieving pain relief” as reported in a Cochrane review (6) in order to report the likelihood of achieving pain relief. This conversion was incorrect because relative risk is not a symmetric statistic. The evidence review (2) is now corrected, stating results as originally reported in the Cochrane review: For skeletal muscle relaxants, relative risks for not achieving pain relief were 0.80 (95% CI, 0.71 to 0.89) at 2 to 4 days and 0.67 (CI, 0.13 to 3.44) at 5 to 7 days and relative risks for not achieving global efficacy were 0.49 (CI, 0.25 to 0.95) at 2 to 4 days and 0.68 (CI, 0.41 to 1.13) at 5 to 7 days. For benzodiazepines, relative risks were 0.71 (CI, 0.54 to 0.93) for not achieving pain relief at 8 to 14 days and 0.63 (CI, 0.42 to 0.97) for not achieving global efficacy at 8 to 14 days (6). Similarly, in the evidence review on nonpharmacologic therapies (3), results for a systematic review by Kool and colleagues (7) on exercise therapy should state a relative risk of 0.73 (CI, 0.56 to 0.95) for not returning to work after 1 year. None of these corrections affect the conclusions of the evidence reviews or guidelines.

All corrections have been applied to the online version of the articles.

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Correction: Recommendations for Screening for Carotid Artery Stenosis

In the recent U.S. Preventive Services Task Force recommendation statement on screening for carotid artery stenosis (1), there is an error under the heading “Recommendations of Other Groups.” The first sentence should read: “In 2006, the American Heart Association/American Stroke Association did not recommend screening the general population for asymptomatic carotid stenosis.”

Reference
### Appendix Table 1. Keywords and Journals Searched

**Genetic discovery terms**
- allele
- allelic
- breakpoint
- characteris
- characterize
- clone
- cloning
- deficienc
- delet
- disrupt
- encod
- fami
- frameshift
- frame-shift
- frame shift
- gene
- genes
- genetic
- genomic
- germ line
- germine
- germ-line
- haplotype
- hereditary
- identif
- inherit
- insertion
- linkage
- loci
- locus
- mapp
- missense
- mutant
- mutat
- polymorph
- sequenc
- transition
- transversion
- variant

**Journals searched**
- American Journal of Human Genetics
- Annual Review of Genetics
- Cell
- Current Biology
- Developmental Cell
- DNA Repair
- EMBO Journal
- EMBO Reports
- Faseb Journal
- Genes & Development
- Genetic Epidemiology
- Genome Biology
- Genome Research
- Journal of the American Medical Association
- Journal of Biological Chemistry
- Journal of Cell Biology
- Journal of Cell Science
- Journal of Clinical Investigation
- Journal of Experimental Medicine
- The Lancet
- Molecular Biology of the Cell
- Molecular Cancer Research
- Molecular Cell
- Molecular Cell Biology
- Molecular Psychiatry
- Nature
- Nature Cell Biology
- Nature Genetics
- Nature Medicine
- New England Journal of Medicine
- Nucleic Acids Research
- Oncogene
- Pharmacogenetics
- Proceedings of the National Academy of Sciences of the United States of America
- Science
### Appendix Table 2. Studies Identifying Genetic Determinants of Disease

<table>
<thead>
<tr>
<th>Study, Year (Reference)</th>
<th>Times Cited, ( n )</th>
<th>Disease</th>
<th>Gene Symbol</th>
<th>Translation to Trials</th>
<th>Translation to Approved Therapies (Drugs)</th>
</tr>
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<tbody>
<tr>
<td>Zhang et al., 1994 (5)</td>
<td>4831</td>
<td>Obesity</td>
<td>LEP</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Riordan et al., 1989 (6)</td>
<td>3471</td>
<td>Cystic fibrosis</td>
<td>CFTR</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Corder et al., 1993 (7)</td>
<td>3101</td>
<td>Alzheimer disease</td>
<td>APOE</td>
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<td>–</td>
</tr>
<tr>
<td>Miki et al., 1994 (8)</td>
<td>2566</td>
<td>Breast/ovarian cancer</td>
<td>BRCA1</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Bertina et al., 1994 (9)</td>
<td>2471</td>
<td>Activated protein C resistance</td>
<td>F5</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Nigro et al., 1989 (10)</td>
<td>2421</td>
<td>Multiple human malignant conditions</td>
<td>TP53</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Ullrich et al., 1984 (11)</td>
<td>2179</td>
<td>Epidermoid carcinomas</td>
<td>EGFR</td>
<td>Yes</td>
<td>Yes ( cetuximab)</td>
</tr>
<tr>
<td>Rosen et al., 1993 (12)</td>
<td>2162</td>
<td>Familial amyotrophic lateral sclerosis</td>
<td>SOD1</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Cole et al., 1992 (13)</td>
<td>1986</td>
<td>Multidrug resistance</td>
<td>ABCC1</td>
<td>–</td>
<td>–</td>
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<tr>
<td>Vaux et al., 1988 (14)</td>
<td>1953</td>
<td>Follicular lymphoma</td>
<td>BCL2</td>
<td>No</td>
<td>No</td>
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<tr>
<td>Malkin et al., 1990 (15)</td>
<td>1950</td>
<td>Li-Fraumeni syndrome</td>
<td>TP53</td>
<td>–</td>
<td>–</td>
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<tr>
<td>Feder et al., 1996 (16)</td>
<td>1905</td>
<td>Hereditary hemochromatosis</td>
<td>HLA-H</td>
<td>–</td>
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<tr>
<td>Polymorphous et al., 1997 (17)</td>
<td>1881</td>
<td>Parkinson disease</td>
<td>SNCA</td>
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<tr>
<td>Fishel et al., 1993 (18)</td>
<td>1825</td>
<td>Hereditary nonpolyposis colon cancer</td>
<td>MSH2</td>
<td>–</td>
<td>–</td>
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<tr>
<td>Bertina et al., 1994 (9)</td>
<td>1809</td>
<td>Alzheimer disease</td>
<td>PSEN1</td>
<td>–</td>
<td>–</td>
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<tr>
<td>Li et al., 1997 (20)</td>
<td>1635</td>
<td>Brain/breast/prostate cancer</td>
<td>PTEN</td>
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<td>Huntington’s Disease Collaborative Research Group, 1993 (21)</td>
<td>1572</td>
<td>Huntington disease</td>
<td>HD</td>
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<td>Morin et al., 1997 (22)</td>
<td>1551</td>
<td>Colorectal cancer</td>
<td>CTNNB1, APC</td>
<td>–</td>
<td>–</td>
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<td>Todd et al., 1987 (23)</td>
<td>1509</td>
<td>Type 1 diabetes mellitus</td>
<td>HLA-DQB1</td>
<td>–</td>
<td>–</td>
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<tr>
<td>Fearon et al., 1990 (24)</td>
<td>1461</td>
<td>Colorectal cancer</td>
<td>DCC</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Cambien et al., 1992 (25)</td>
<td>1440</td>
<td>Myocardial infarction</td>
<td>ACE</td>
<td>Yes</td>
<td>Yes (renin-angiotensin system inhibitors)</td>
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<td>Savitsky et al., 1995 (26)</td>
<td>1393</td>
<td>Ataxia-telangiectasia</td>
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<td>Bronner et al., 1994 (27)</td>
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<td>Hereditary nonpolyposis colon cancer</td>
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<td>Nobori et al., 1994 (28)</td>
<td>1369</td>
<td>Various malignant conditions</td>
<td>CDKN2A</td>
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<td>Hayward et al., 1981 (29)</td>
<td>1335</td>
<td>Lymphoma</td>
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<td>1327</td>
<td>Duchenne muscular dystrophy</td>
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<td>Bos et al., 1987 (31)</td>
<td>1316</td>
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<td>Oliner et al., 1992 (32)</td>
<td>1301</td>
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<td>Pancreatic carcinoma</td>
<td>SMAD4</td>
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<td>Li et al., 1996 (34)</td>
<td>1275</td>
<td>HIV resistance</td>
<td>CCR5</td>
<td>Yes</td>
<td>No</td>
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<td>Call et al., 1990 (35)</td>
<td>1266</td>
<td>Wilms tumor</td>
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<td>Fojo et al., 1987 (36)</td>
<td>1257</td>
<td>Multidrug resistance</td>
<td>ABCC1</td>
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<td>Wooster et al., 1995 (37)</td>
<td>1249</td>
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<td>Feng et al., 1995 (38)</td>
<td>1233</td>
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<td>TERC</td>
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<td>Lesch et al., 1996 (40)</td>
<td>1173</td>
<td>Anxiety traits</td>
<td>SLC6A4</td>
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<td>Yes (serotonin uptake modulators)</td>
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<td>Latif et al., 1993 (41)</td>
<td>1142</td>
<td>von Hippel–Landau disease</td>
<td>VHL</td>
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<td>Retinoblastoma</td>
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<td>1119</td>
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<td>Alzheimer disease</td>
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<td>Bladder carcinoma</td>
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<td>Yes (vitamin D analogues)</td>
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<td>1040</td>
<td>Alzheimer disease, Down syndrome</td>
<td>APP</td>
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<td>Orr et al., 1993 (53)</td>
<td>1038</td>
<td>Spincerebellar ataxia type 1</td>
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<td>Libermann et al., 1985 (54)</td>
<td>1025</td>
<td>Glial brain tumors</td>
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<td>Smith et al., 1994 (55)</td>
<td>1014</td>
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<td>Leber hereditary optic neuropathy</td>
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<td>Mulligan et al., 1993 (57)</td>
<td>1005</td>
<td>Multiple endocrine neoplasia type 2A</td>
<td>RET</td>
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<td>Yes (sunitinib)</td>
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