Am. J. Hum. Genet. 59:301–307, 1996

Cost Comparison of Molecular versus Conventional Screening of Relatives at Risk for Retinoblastoma

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Summary

To compare costs of molecular and conventional screening of retinoblastoma relatives, we evaluated the direct health care costs. With variables set at the most likely values (baseline), the expected cost (in 1994 Canadian dollars) of conventional screening was $31,430 for a prototype family consisting of seven at-risk relatives (three clinic exams and eight examinations under anaesthetic over the first 3 years of life for each relative). For the molecular strategy that involves looking for the *RB1* gene mutation in the proband, testing the relatives for that mutation, and clinical follow-up similar to conventional strategy for relatives with mutation, the expected cost was $8,674, using baseline variables. Sensitivity analysis over the range of values for each variable revealed a significant saving of health care dollars by the molecular route, indicating the benefit of redirecting economic resources to molecular diagnosis in retinoblastoma.

Introduction

Retinoblastoma is a childhood cancer of the retina, affecting ~1 in 20,000 live births (Tamboli et al. 1990), which is often present at birth (Musarella and Gallie 1987; Draper et al. 1992) but may develop in the first 4 years of life. Both hereditary and nonhereditary retinoblastoma result from inactivation of both alleles of the tumor-suppressor gene, *RB1* (Comings 1973; Cavenee et al. 1983). Nonhereditary retinoblastoma arises when both alleles are mutated in a single developing retinal cell. The hereditary predisposition to retinoblastoma results from germ-line mutation of one *RB1* allele, transmitted as an autosomal dominant trait with usually high penetrance (Matsunaga 1976; Bonaïti-Pellié and Briard-Guillemot 1981; Lohmann et al. 1994*a*). Somatic loss of the second *RB1* allele results in a high incidence of bilateral tumors and a risk for mesenchymal tumors in early adult life (Eng et al. 1993).

The *RB1* gene (Friend et al. 1986; McGee et al. 1989) spans 180 kb, divided into 27 exons with promoter sequence within 1.5 kb (Gill et al. 1994). Until recently, the appearance of tumors was the most effective way to identify *RB1* mutation carriers in families, necessitating repeated ophthalmological examinations under general anaesthetic (EUA) for the first 3 years of life (Musarella and Gallie 1987), of all children who are close relatives of affected individuals. Early diagnosis of retinoblastoma tumors makes possible low-morbidity treatment (focal therapy with laser and cryotherapy), while delayed diagnosis necessitates surgery (removal of one or both eyes) and chemotherapy and radiation to try to save vision (Gallie et al. 1991). Although most retinoblastoma tumors are the result of new unique mutations in *RB1* in the affected child (Dunn et al. 1989), parents and grandparents can be unaffected mutation carriers (Bonaïti-Pellié and Briard-Guillemot 1981). Therefore, the siblings, nephews/nieces, and first cousins of bilaterally affected individuals are conventionally recommended for screening by repeated EUA as the international standard of care for retinoblastoma.

The *RB1* mutation in most families can be determined by molecular analysis, permitting accurate genetic counseling. Once the mutation is identified, blood from family members can be tested to determine which new infants require the conventional clinical surveillance in order to detect and treat tiny retinoblastoma tumors before they damage vision. Because of reduction in diagnostic uncertainty and necessity for clinical examinations, since only a small number of relatives will actually carry the mutation, better health outcomes and lower costs might be expected under the molecular strategy. However, new technologies in medicine have frequently been expensive.

We report a comparison from the perspective of a third-party payer, of the costs of a sequence-based strategy for molecular identification of *RB1* mutations with the costs of conventional screening to detect tumors. We

Received February 1, 1996; accepted for publication May 22, 1996.

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0002-9297/96/5902-0005$02.00

measured and valued all direct health care costs through detailed monitoring and data collection and used the method of decision analysis (Kassirer et al. 1987; Sox et al. 1988) to evaluate the expected costs of the comparative strategies.

Material and Methods

Molecular Mutation Identification

We evaluated the costs of identification of the *RB1* mutation in blood of bilateral and familial retinoblastoma families by the molecular technology in use in 1994 in our laboratory. The direct costs measured for molecular screening were personnel time, including technician labor and genetic counseling; supplies; equipment; and overhead. All samples being analyzed at the time were monitored in detail, and sample analysis was simulated following the protocols. Labor costs were valued on the basis of the technicians' actual gross annual earnings, including benefits, and adjusted to account for holiday and sick leave. Supplies (e.g., chemicals, solutions and buffers, and disposables) were valued on the basis of replacement prices. All the materials consumed were valued, including an estimate of wastage. All essential laboratory equipment were valued using current replacement costs, on an "annualized" (Cleverley 1989) basis using a 5% discount rate (Krahn and Gafni 1993), with an assumed working life of 3 years. Equipment costs per sample were derived by estimating the optimal laboratory caseload. Twenty percent of the total costs per sample was allocated to overhead, accounting for utilities, lab licensing, and other operating inputs not identified above, including freight.

Although formal counseling was not routinely performed at the time of this cost comparison, the average time commitment (direct and indirect contact) required was estimated to be 3 h of contact time (e.g., pretest explanation, informed consent, test reporting, and discussion of results) per affected individual (proband), and 2 h for each at-risk relative. Counseling time was valued using the (adjusted) salary grade for genetic counselors.

Conventional Screening for Retinoblastoma Tumors

The 1994 clinical management of retinoblastoma families at Toronto's Hospital for Sick Children (HSC) was observed and costs evaluated. The inputs valued for conventional screening were personnel time, other recurrent inputs, equipment, and overhead. Physician fees (surgeon, anaesthetist), including the cost for the genetic assessment, were derived from the Ontario Ministry of Health Schedule of Benefits (1992). Each equipment unit (e.g., indirect ophthalmoscope, electrocardiogram, anaesthetic gas analyzer) was used for $\frac{1}{2}$ h per procedure and valued on a annualized basis, using a 5-year working life and a 5% discount rate. Twenty percent of the total procedure costs for the examinations without anaesthetic and 33% of costs for the EUAs were allocated to overhead, accounting for utilities, administrative and support services, and use of clinic space.

For the examinations without anaesthetic, performed at the Ophthalmology Clinic at birth and to age 3 mo, the ophthalmic assistant time per procedure ($\frac{5}{6}$ h, on the basis of two patients) was valued using the adjusted actual gross annual earnings of the ophthalmic assistant. Other recurrent inputs (e.g., ancillary salaries and supplies) were valued using the clinic budget for the 1993–94 fiscal year. For the EUAs performed at the ambulatory clinic from age 3 mo to age 3 years, nursing (preoperative, operating room, recovery, and discharge) and ophthalmic assistant times were monitored for each of six patients undergoing EUAs in 1994 and allocated per procedure. The (adjusted) salary grade for nurses was used for valuation purposes. Supplies (e.g., drugs and solutions, disposables including electrocardiogram pads and endotracheal tubes, and nondisposables) were measured through detailed monitoring of 16 procedures and valued using current market prices. Nondisposable supplies were measured on the basis of their optimal useful life in terms of caseload. Operating room "set-up" costs (including personnel time) for each EUA were determined using hospital schedule rates for the 1993–94 fiscal year and adjusted to account for an estimate of the "true" costs using a cost-to-charge ratio. Since infant relatives are examined every 2–6 mo within this time period, a discount rate equivalent to 5% per annum (Krahn and Gafni 1993) was applied to the total costs for each subsequent procedure following the initial EUA.

Baseline Analysis

We constructed a decision-analysis model to compare the molecular and conventional strategies for screening of relatives (fig. 1). The two options (molecular, upper branch; conventional, lower branch) are located at the square decision node. For either screening strategy, the circular nodes represent events that may occur by chance. For the molecular strategy, the initial chance event (*pSens*) was finding or not finding the *RB1* mutation in the proband; if it was found, at-risk relatives were screened for that mutation. If the mutation was not found in the proband, the relatives were screened using the conventional strategy. For both conventional and molecular strategies, the tree had a similar structure thereafter. Four categories of relatives were identified: offspring, siblings, nephews/nieces, and first cousins. Subsequent nodes represent the following chance events: the risk of carrying the *RB1* mutation (*pCarry*), the degree of expression of the *RB1* mutation (*pExp*), and the probability of detecting retinoblastoma (RB) tumor(s) at age 1 year (*p1yr*) and age 3 years (*p3yr*). The outcome measures evaluated in the model were

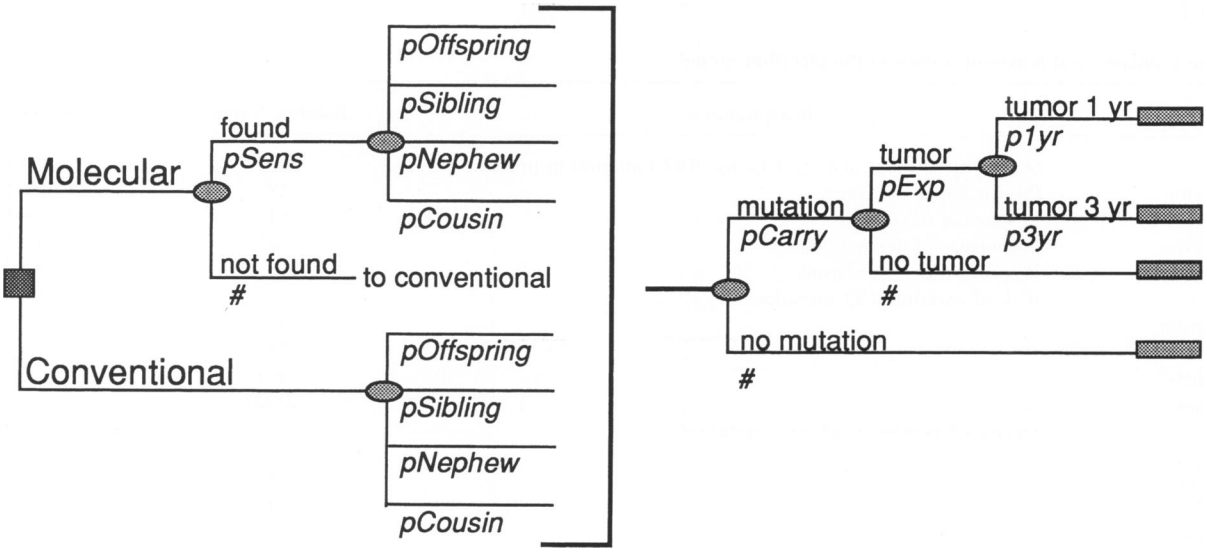

Figure 1 Decision model. The square node at left indicates the initial decision regarding screening. Circular nodes represent chance events, and rectangular nodes outcomes corresponding to that path in the decision tree. The bracket indicates that branches ending at the bracket enter the subtree, depicted to the right of the bracket. A pound sign (#) represents complementary probability.

direct health care costs. The model was constructed and evaluated using the software program SMLTREE (Hollenberg 1989).

Eight major assumptions were made in our model to simplify the analysis yet retain the basic issues: (1) a prototypical family consisted of one bilaterally affected patient and seven at-risk relatives, on the basis of enumeration of the families at HSC; (2) the patient was the first bilaterally affected member of a family with no history of retinoblastoma with a new germ-line mutation and a 10% chance of an inherited mutation; (3) the relatives requiring screening consist of two offspring, one sibling, two nephews/nieces, and two first cousins; (4) the molecular strategy is 90% sensitive for the *RB1* mutation in the proband (authors' unpublished data); (5) the molecular strategy is perfectly accurate for the known *RB1* mutation in relatives of the proband (error in blood sample can not be ruled out, but second samples can be checked but were not included in our costs); (6) 95% of retinoblastoma tumors are detected by age 1 year, and 100% of tumors by age 3 years; (7) the age at screening onset for each relative was birth; and (8) the time horizon for conventional screening was 3 years (95% of hereditary cases are diagnosed prior to age 3 years [Draper et al. 1992]).

The baseline probability values used in the decision model and range of plausible values are summarized in table 1. The range of values for carrying the *RB1* mutation (.0005–.50) are risk estimates for relatives (Musarella and Gallie 1987). Because of autosomal dominant transmission, the offspring of a bilateral proband have a .50 (50%) chance of inheriting *RB1* mutations. The risk for a sibling, nephew, or first cousin depends on the number of apparently unaffected individuals intervening between the proband and the person in question, who each have a .1 risk of carrying the mutation (Musarella and Gallie 1987). For example, siblings of a proband with unaffected parents have a risk of .05 (.5 × .1). The risk of actually developing tumors can be obtained by multiplying the risk of having the *RB1* mutation (*pCarry*) by a factor based on the degree of expression (*pExp*) of the mutation in the parent (Musarella and Gallie 1987). If the parent was bilaterally affected, likelihood of expression in the offspring with the mutation is .90; if the parent is unaffected, likelihood of expression in the offspring with the mutation is .54 (Matsunaga 1976; Bonaïti-Pellié and Briard-Guillemot 1981; Lohmann et al. 1994*a*).

Sensitivity Analysis

We examined all key variables of the model over a wide range of values. Using sensitivity analysis, we determined threshold (point at which two strategies have equal expected costs) for the following variables: the number of at-risk relatives in a family (1–10); the molecular sensitivity for the *RB1* mutation in the proband (.00–1.00); the proportion of relatives being offspring (.00–1.00); the proportion of relatives being first cousins (.00–1.00); and the proband cost under the molecular strategy ($600–$15,600).

Results

Detection of RB1 Mutations

Documented *RB1* mutations fall into three broad classes: (1) small deletions, insertions, and/or rearrange-

Table 1

Baseline Estimates and Range of Values in the Decision Model

Variable	Interpretation	Baseline Value	Plausible Range
pSens	Sensitivity of molecular strategy for *RB1* mutation in proband	.90	.00–1.00[a]
pOffspring	Proportion of offspring	.28[b]	.00–1.00[a]
pSibling	Proportion of siblings	.14[c]	.00–1.00[a]
pNephew	Proportion of nephews/nieces	.28[b]	.00–1.00[a]
pCousin	Proportion of first cousins	.28[b]	.00–1.00[a]
pCarry:	Risk of carrying *RB1* mutation		.0005–0.50[d]
Offspring		.50	
Sibling		.05	
Nephew		.005	
Cousin		.0005	
pExp:	Degree of expression of *RB1* mutation		.33–1.00[e]
Offspring		.90	
Sibling		.54	
Nephew		.54	
Cousin		.54	
p1yr	Detection of retinoblastoma tumor(s) at age 1 year	.95	.00–1.00[e]
p3yr	Detection of retinoblastoma tumor(s) at age 3 years	1.00	.00–1.00[e]

NOTE.—The notations correspond to the probabilities associated with each chance event in the decision model.
[a] Authors' estimates.
[b] Two of seven relatives.
[c] One of seven relatives.
[d] Estimated from Musarella and Gallie (1987).
[e] Estimated from Matsunaga (1976); Bonaïti-Pellié and Briard Guillemot (1981); Lohmann et al. (1994*a*).

ments; (2) missense or nonsense point mutations; and (3) translocations (Dunn et al. 1989; Lohmann et al. 1992, 1994*b*; Blanquet et al. 1995). Detection of each of these mutation classes requires a different technique. In the molecular strategy that we evaluated for costs, the 27 exons and the promoter region in DNA from blood of bilateral or familial retinoblastoma patients were first screened by "fragment analysis," consisting of quantitative multiplex PCR to examine the length and copy number of exon/promoter fragments. This technique detected large deletions (whole exons and multiple exons) and small deletions and insertions (as small as 1 bp), which were confirmed by sequencing (authors' unpublished data; Lohmann et al. 1992). If no *RB1* mutation was detected by this screen in a sample, the 27 exons and the promoter region were sequenced until a definite mutation was found. Sequence variations that could be polymorphisms without producing disease were recorded, but study of the remainder of the gene was continued. If the suspected mutation would yield an in-frame rearrangement, further functional tests were carried out on that allele before it was considered the disease-causing mutation. Since this is a rare and highly variable occurrence, these tests were not evaluated for cost. In the absence of this detailed confirmation of the mutation, it is considered that the *RB1* mutation has not been detected in the proband. Both of these screens were performed using the Automated Laser Fluorescent (ALF) DNA Sequencer from Pharmacia LKB and software developed by Visible Genetics.

Some translocations will be missed using these screens but will be detected by FISH (Barr et al. 1995), which is applied to samples appearing normal on all the previous tests. Since only 5% of *RB1* mutations will require FISH, this technique was not included in the cost analysis. From pilot data on 170 patients, it is expected that this strategy will identify the *RB1* mutations in >90% of patient samples analyzed (data not shown). More than 50% of the *RB1* mutations in these patients have been detected by fragment analysis alone; sequencing of exons and promoter is revealing a significant fraction of the remainder of mutations. Once the precise *RB1* mutation was identified in a patient, at-risk family members were easily and accurately tested for that mutation, allowing the majority of the infant relatives to be excluded from further clinical monitoring.

The direct costs of molecular screening for the proband and each at-risk family member are indicated in table 2. Technician labor constituted >50% of the total recurrent costs. The cost of the initial identification of the family's mutation in the proband was sixfold greater than the cost of subsequently testing each at-risk relative for the proband's mutation.

Conventional Screening

Since all cases, even nonfamilial unilateral cases, might be heritable (Musarella and Gallie 1987; Gallie

Table 2

Molecular Screening Costs

Test (Input)	Cost/Test[a]	Average No. of Tests	Cost/Sample[a]
Proband:			
DNA extraction[b]	11.87	1	11.87
Fragment analysis[b]	10.21	8	81.68
Sequencing[b]	28.52	15	427.80
(Equipment)			477.02
(20% overhead)			199.67
(Genetic counseling)			91.56
			1,289.60
Relative:			
DNA extraction[b]	11.87	1	11.87
Sequencing[b]	28.52	2	57.04
(Equipment)			67.02
(20% overhead)			27.19
(Genetic counseling)			61.04
			224.16

[a] Values are expressed in 1994 Canadian dollars.
[b] Costs per test include technician labor and supplies.

et al. 1991), at HSC infant relatives of all affected patients are screened. Conventional screening consists of complete retinal examination without anaesthetic, at birth and every 6 wk until 3 mo of age (three exams total), and EUA at 5, 7, 9, 12, and 16 mo, and every 6 mo to age 3 years (eight EUAs total) (Musarella and Gallie 1987). Subsequently, semiannual or annual examinations are recommended, depending on the risk for retinoblastoma (Musarella and Gallie 1987). These examinations are certain to identify the pathognomonic tumors (Gallie et al. 1991).

The direct costs of conventional screening for each at-risk relative for the first 3 years of life are shown in table 3. Costs per procedure were significantly higher for the EUAs than for the examinations without anaesthetic. Personnel expenses, operating room "set-up" costs, and overhead all contributed to this greater consumption of resources. Personnel expenses made up >50% of the total costs for the examinations without anaesthetic, and over one-third of the EUA costs.

Baseline Analysis

With each of these variables set at baseline (most likely value), screening of a prototype family consisting of one proband and seven at-risk relatives cost $8,674, including identification of the *RB1* mutation in the proband, subsequent testing of the relevant relatives for that mutation, and clinical follow-up similar to the conventional strategy for relatives with mutation. If *RB1* mutation is not found in the proband, then those relatives require conventional exams. This factor is also accounted for in the above cost estimate. For the same family, each of the seven at-risk infants would conventionally undergo three clinic visits and eight EUAs over the first 3 years of life, for a cost of $31,430 (in 1994 Canadian dollars).

Sensitivity Analysis

The molecular screening strategy was less expensive over the full ranges of values for the number of at-risk relatives and the proportion of relatives that are offspring or first cousins (table 4). Holding each of the other baseline variables constant, the molecular strategy was cost saving even if the number of at-risk relatives in a family was only one. For the molecular route to cease being cost saving, the test sensitivity for the proband had to fall below .05, or the proband mutation identification cost had to exceed $12,152.

Discussion

As mutations in genes are implicated in specific diseases, molecular technology makes prediction of disease feasible. However, genetic diagnosis raises important ethical and economic concerns. The ethical issues of molecular diagnosis of the presence of an *RB1* mutation in a infant seem relatively minor, since effective therapy is available to treat retinoblastoma tumors when they are discovered early, preventing blindness and death. In the past, screening strategies have often become standards of care without undergoing rigorous cost analysis. We performed detailed monitoring to determine whether molecular or conventional screening for bilateral retinoblastoma is less costly. Using the perspective of a third-party payer, the molecular route costs fourfold less than conventional for a prototypical family at risk for retinoblastoma.

Our analysis as a whole is conservative. The assumption made about the time horizon for conventional screening is extremely conservative, since at-risk relatives continue to be examined subsequent to age 3 years, on a semiannual or annual basis up to at least 6 years of age (Musarella and Gallie 1987; Draper et al. 1992). Sensitivity analyses demonstrate that the molecular strategy is cost saving over a wide range of values for key variables (table 4). Since the threshold (Pauker and Kassirer 1980) values of 5% test sensitivity and proband molecular costs in excess of $12,152 are outside the likely ranges, our conclusions are robust. Even for a small family with a single at-risk relative there is a significant saving of health care dollars by the molecular route. For large families, savings are greater: in a four-generation family with 25 at-risk children at the present time, in which the mutation has just been discovered (unpublished data of B. L. Gallie), the savings are 16-fold. Since our perspective was that of a third-party payer, only the costs directly related to the comparative

Table 3

Conventional Screening Costs

Input	Cost/Exam[a]	Recommended No. of Exams	Cost/Patient[a]
Birth to age 3 mo:			
Personnel	48.53		
Other recurrent/equipment	20.54		
20% overhead	13.81		
	82.88	3	248.64
Age 3 mo to age 3 years [EUA]:			
Physician fees	142.80		
Other personnel	83.25		
Supplies	21.52		
Equipment	3.10		
Operating room set-up	188.00		
33% overhead	144.76		
	583.43	8	4,458.43[b]
Genetic assessment			55.90
			4,762.97

[a] Values are expressed in 1994 Canadian dollars.
[b] Five percent discount rate.

strategies were considered. Inclusion of direct personal and indirect costs, such as lost productivity of accompanying family members during each hospital visit, would result in even greater cost savings under the molecular route.

Our analysis is solely a cost comparison and thus did not consider or evaluate the clinical outcomes of the comparative strategies, since the retinoblastoma tumors should be detected at the same time by either strategy. A utility analysis (Torrance 1987) to assess family preferences for the molecular and conventional strategies is the subject of future research. Apart from the lower cost, we anticipate that the molecular route will be preferred over the conventional: the normal children can be spared the frequent, invasive, stressful ophthalmological examinations, while those with mutations and at very high risk of developing tumors can be followed with increased vigilance, in order to avoid blindness or the need for surgery, radiotherapy, or chemotherapy (Gallie et al. 1991). It seems likely that the molecular strategy would strongly "dominate" (Keeney and Raiffa 1976) the conventional strategy by improving outcomes and saving resources.

What are the policy implications of this analysis? Since the alternative to molecular detection of the *RB1* mutation is the more expensive repeated ophthalmological examination of infant relatives for at least the first 3 years of life, our analysis indicates the benefit of redi-

Table 4

Sensitivity Analyses on Selected Variables

Variable	Baseline Value	Range of Values	Threshold Value[a]
No. of at-risk relatives in a family	7	1–10	Not found[b]
pSens[c]	.90	.00–1.00	.05
pOffspring[c]	.28	.00–1.00	Not found[b]
pCousin[c]	.28	.00–1.00	Not found[b]
Proband cost under the molecular strategy (in 1994 Canadian dollars)	1,290	600–15,600	12,152

[a] The threshold (Pauker and Kassirer 1980) value is a value where the two strategies have equal expected costs. If a given variable has a value less than a threshold value, then one strategy is cheaper; if the variable has a value greater than a threshold, then the alternative strategy is cheaper.
[b] The molecular strategy is cost saving over all the given values.
[c] The notations correspond to probabilities in the decision model.

recting economic resources to the molecular strategy for identification of mutations in the *RB1* gene. Preliminary data from a similar study of screening for colon cancer (Noorani et al. 1995) does not show a similar magnitude of cost reduction by the molecular strategy studied, indicating that each disease gene must be individually evaluated in terms of current technology, clinical care, and treatment outcomes.

Acknowledgments

We are grateful to Jeffrey D. Sherman of Visible Genetics for his helpful suggestions. This study is supported by grant 72252 (formerly 72148) from the Canadian Genetic Diseases Network, Networks of Centers of Excellence; the National Cancer Institute of Canada with funds from the Terry Fox Run; the Retinoblastoma Family Association; and the Royal Arch Masons of Canada. A.S.D. is supported in part by a National Health Research Scholar Award from Health and Welfare Canada.

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