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Address for correspondence and reprints: Dr. Rosaria Scozzari, Dipartimento di Genetica e Biologia Molecolare, Università "La Sapienza," P. le Aldo Moro 5, 00185 Roma, Italy. E-mail: rscozzar@axcasp.caspur.it
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Diagnostic Testing: A Cost Analysis for Prader-Willi and Angelman Syndromes

To the Editor:

Recently, two different approaches were described by the American Society of Human Genetics/American College of Medical Genetics Test and Technology Transfer Committee (ASHG/ACMG) (1996) regarding the molecular diagnosis of Prader-Willi syndrome (PWS) and Angelman syndrome (AS). It was recommended that individual laboratories use an approach based on a number of factors, including the local availability of testing, previous results for specific patients, and the level of

diagnostic expertise of the referring physician. With the rising cost of medical care and the need to manage cost in all areas of health care, we propose that cost also be considered a factor.

We considered three approaches for molecular diagnostic testing of these syndromes. Approach IA is the same as approach I described by the ASHG/ACMG (1996) and begins with methylation studies. Normal methylation results essentially rule out PWS and most AS. If methylation results are positive, FISH and PCR can be used to determine whether deletion, uniparental disomy (UPD), or imprinting mutations are present. If a 15q11-q13 deletion is present, a parental karyotype is obtained (paternal for PWS, maternal for AS) to identify any parental chromosome abnormality. The second approach, IB, is an alternative to approach IA and begins with FISH studies. A 15q11-q13 deletion by FISH confirms PWS or AS. Parental karyotypes can then be obtained as described above. Negative FISH results are followed by methylation studies. Positive methylation results confirm a diagnosis of PWS or AS, depending on which parental allele is missing, and should be followed by PCR to identify UPD and imprinting mutations. The third strategy is approach II as described by the ASHG/ACMG. The order of tests to be performed in this approach, as described in the ASHG/ACMG report, is not intrinsically clear to the reader. For the sake of this discussion, we assumed that FISH and methylation studies are performed simultaneously in approach II. Normal methylation and FISH results rule out PWS and most AS. Abnormal methylation with normal FISH results should be followed by PCR, to distinguish UPD and imprinting mutations. Positive FISH results should be followed by a parental karyotype.

Smith et al. (1995) suggested that FISH replace the high-resolution karyotype in the diagnosis of PWS and AS because a high-resolution karyotype is less reliable than FISH in detecting deletions in PWS and AS. In addition, they recommended a routine karyotype for all patients, to identify other chromosome abnormalities. DNA studies in those with negative FISH studies were recommended only if the clinical diagnosis was reconfirmed. This approach is similar to approach IB.

Consensus of diagnostic criteria for PWS (Holm et al. 1993) and AS (Williams et al. 1995) have been proposed. When Holm's criteria (Holm et al. 1993) for PWS are met, a molecular mutation (deletion, UPD, or imprinting) can be identified in 96%–97% of patients (Robinson et al. 1991; Gillissen-Kaesbach et al. 1995). In the study done by Gillissen-Kaesbach (1995), the patients who did not meet Holm's criteria had negative molecular studies. While a score of ≥ 8 points, according to Holm's criteria, is considered "typical" PWS, Erdel et al. (1996) found that 30% of patients with 5 or 6 points ("suspected" PWS) had positive molecular stud-

ies. One study of infants with severe hypotonia of unknown etiology (age 0–12 mo) identified PWS in 45% by use of molecular techniques (Gillissen-Kaesbach et al. 1995).

As in the ASHG/ACMG (1996) statement, we assumed that 70% of PWS patients have 15q11-q13 deletions, 28% have maternal UPD, and 2% have imprinting mutations. We also assumed that 70% of AS patients have 15q11-q13 deletions, 4% have paternal UPD, 8% have imprinting mutations, and the remainder have point mutations. We calculated the charges of laboratory testing for the three approaches based on 100 patients, with varying percentages (0%, 25%, 50%, 75%, and 100%) of referred patients actually being affected with PWS or AS (figs. 1 and 2). Patients falling in the 0% affected group would not meet diagnostic criteria; therefore, it is unlikely that a molecular mutation would be detected in these patients. Patients falling in the 100% affected category meet the diagnostic criteria and are likely to have a mutation resulting in PWS or AS. We used our current charges for FISH and methylation analyses (\$200 and \$300, respectively) to calculate the cost of each approach. These charges may differ at other laboratories but are generally reflective of most laboratories. Because a GTG-banded karyotype is obtained for all patients, this cost is constant and therefore does not affect the results. As the percentage of affected patients falls below 50%, approach IA becomes increasingly eco-

nomical (figs. 1 and 2). This is because negative methylation results rule out PWS and most cases of AS, thereby eliminating the need for further laboratory testing. As the number of affected patients approaches 0%, the likelihood of negative methylation results increases. Most laboratories receive referrals from geneticists as well as general pediatricians; therefore, the percentage of referrals for PWS/AS that are positive is most likely <50%. For these laboratories, approach IA would be indicated. Approach IB becomes more economical as the percentage of affected patients increases beyond 50% (figs. 1 and 2) because methylation studies (which are more expensive than FISH) are done only when FISH results are negative. As the percentage of affected patients approaches 100%, the likelihood of detecting a deletion increases, reducing the need to perform both FISH and methylation studies. In all scenarios, approach II is the most costly (figs. 1 and 2) because FISH and methylation studies are done in every case.

We propose that a checklist utilizing the consensus diagnostic criteria discussed above be completed, with clinical features of each patient and included with samples for PWS and AS molecular diagnostic testing. The criteria should be easy to ascertain so that the form can be completed accurately by referring physicians who may not have a lot of experience in recognizing the clinical manifestations of PWS and AS. The checklist should also be brief, to increase the likelihood that the referring

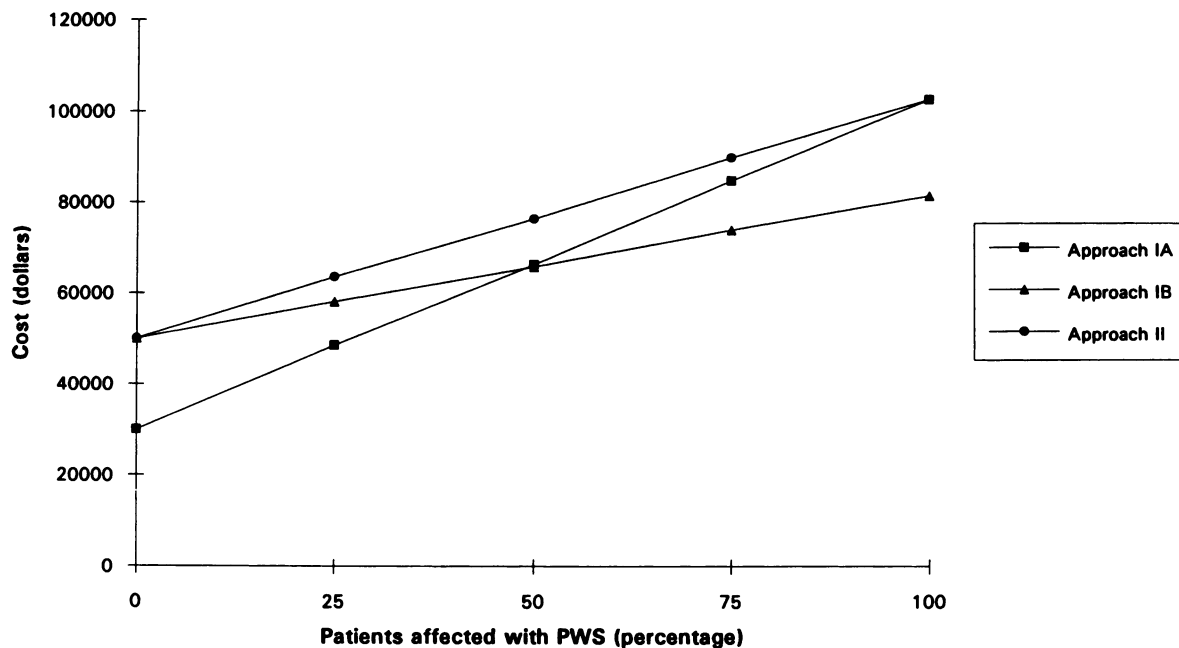


Figure 1 Cost, in dollars, for each diagnostic approach versus the percentage of patients affected with PWS. Approach IA, methylation studies followed by FISH; approach IB, FISH followed by methylation studies; approach II, concurrent FISH and methylation studies. Total cost was calculated on the basis of 100 patients and the current charges at our institution for FISH, methylation, and karyotype analyses (see text).

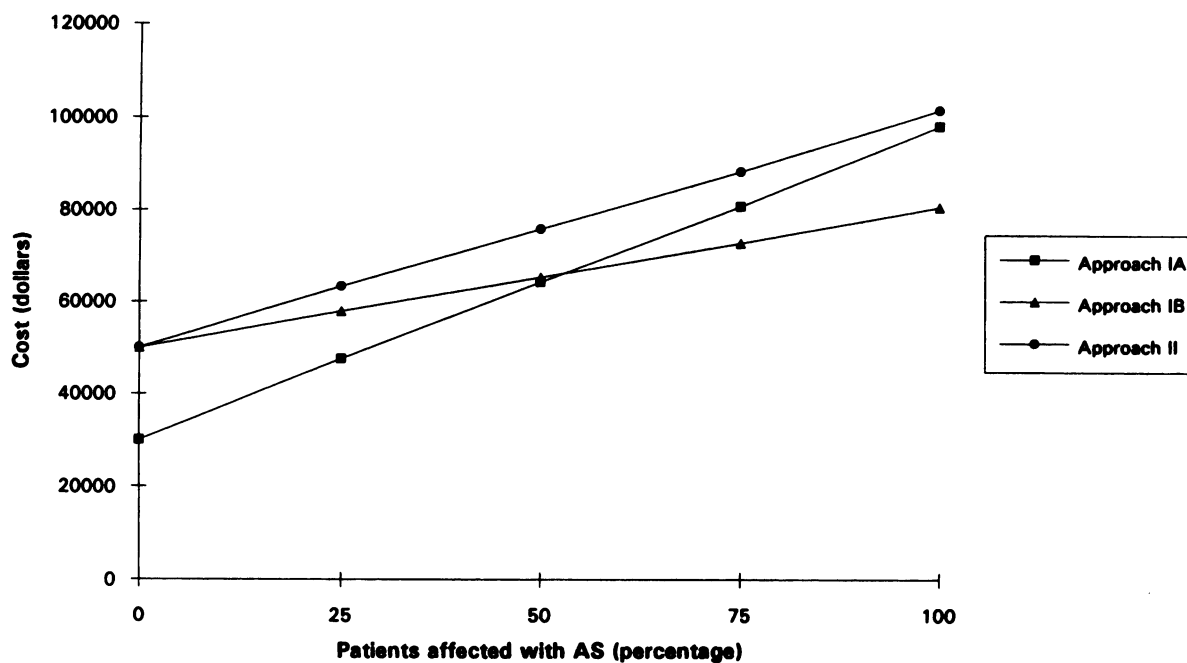


Figure 2 Cost, in dollars, for each diagnostic approach versus the percentage of patients affected with AS. Approach IA, methylation studies followed by FISH; approach IB, FISH followed by methylation studies; approach II, concurrent FISH and methylation studies. Total cost was calculated on the basis of 100 patients and the current charges at our institution for FISH, methylation, and karyotype analyses (see text).

physician would take the time to use the diagnostic scoring system. To assure physician compliance, a laboratory could require the checklist be completed before the studies are performed. The sequence of molecular tests followed would be based on the total number of points scored for individual patients. Approach IB would be followed for PWS patients with ≥ 5 points based on Holm's criteria. For patients with < 5 points, approach IA would be followed. This would save $\sim 20\%$, or \$200.00 per patient. Almost 50% of infants with severe hypotonia of unknown cause (age 0–12 mo) have PWS (Gillesen-Kaesbach et al. 1995). At 50%, the costs of approaches IA and IB are essentially equal, while the cost of approach II is $\geq \$100.00$ more expensive per patient (figs. 1 and 2). Therefore, by following either approach IA or IB instead of approach II when testing for PWS in hypotonic infants, a savings of 14%, or \$105.00 per patient, is achieved. Additional savings would accrue if clinical staff choose to test for PWS or AS only if specific diagnostic criteria are met.

Patient costs are reduced by sequential testing (approaches IA and IB). The cytogenetic and molecular diagnostic laboratories at many institutions work together closely, so it would not be difficult to use approaches IA and IB alternatively. However, concurrent methylation and FISH studies (approach II) result in a faster turnaround time for reporting results. The accelerated diagnosis may make a difference in how some patients

with PWS and AS are managed. For example, without a diagnosis, some infants with PWS may undergo a muscle biopsy for hypotonia or an unnecessary gastrostomy-tube placement for failure to thrive. Therefore, in some situations it may be appropriate to forgo patient cost, to expedite a diagnosis.

It is likely that, as more is learned about the etiology of genetic diseases, additional imprinting mutations will be identified. Therefore, it seems beneficial to develop a strategy for diagnosing this type of disorder. The cost savings achieved by using alternative sequential approaches rather than a single concurrent approach will increase as more imprinting mutations are identified.

KRISTIN G. MONAGHAN, DANIEL L. VAN DYKE,
GERALD FELDMAN, ANNE WIKTOR, AND LESTER WEISS
*Medical Genetics and Birth Defects Center, Henry
Ford Hospital, Detroit*

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Address for correspondence and reprints: Dr. Kristin G. Monaghan, Henry Ford Hospital, 2799 West Grand Boulevard, CFP-4, Detroit, MI 48202-2689.
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