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article

Cost and effectiveness of the California triple marker prenatal screening program

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Purpose: To report the utilization of services offered and pregnancy outcomes for a unique statewide prenatal triple marker screening program and to present a cost-benefit analysis. A state population of 32 million with considerable ethnic and age distribution and with a wide variety of delivery systems providing prenatal care was considered. The entire pregnant population who appeared for care before 20 weeks gestation, approximately one-half million per year during the years of 1995 to 1997, was included in the study. **Methods:** Mandatory offering of serum testing, using alpha-fetoprotein from 1986 to 1995, and the addition of human chorionic gonadotropin and unconjugated estriol in 1995, with systematic follow-up of serum screen positives with ultrasound and amniocentesis. This study collected and analyzed the program data and reports of outcomes and collected similar information from the birth defects registry. **Results:** Triple marker serum screening was accepted by 67.4% of the women eligible and yielded an initial positive rate of 7.3%. More than 90% of the initially screen positive pregnancies were seen at a prenatal diagnostic center. After correction of gestational age, 71.3% had amniocentesis. The overall amniocentesis rate among women screened was 2.6%. The Program's detection rate was predicted to be 85% for neural tube defects, and, based on Monte Carlo modeling, was theoretically calculated to be 62% for Down syndrome. In practice, detection rates were 75% for neural tube defects and 41% for Down syndrome due to lower than expected amniocentesis acceptance rate. Nevertheless, at a 5% discount rate, the screening program was cost beneficial at a ratio of 2.69:1. The cost per case detected was $35,365 and per case prevented was $110,741. **Conclusion:** It is possible to implement a cost-effective population-based screening in compliance with quality standards in a diverse ethnic population with a variety of health-care providers. Triple marker screening in the second trimester is a cost beneficial program even if utilization of all services is less than ideal. ***Genetics in Medicine*, 1999:1(5):200–207.**

Key Words: *Screening, cost/benefit, prevention, birth defects, prenatal care*

With the explosion of knowledge in the field of genetics, public health agencies are beginning to discuss and debate the implications with respect to the traditional areas of public health responsibility. Public health agencies must now consider whether new models and mechanisms are needed to keep public health as an active, responsible participant.[1–3] This article describes a model adopted in California for constructively addressing this challenge and an assessment of the degree to which it has achieved its objectives.

HISTORY OF MSAFP SCREENING

Maternal serum alpha-fetoprotein (MSAFP) screening became a technical possibility when Brock[4] reported elevated AFP in maternal serum from pregnancies with fetuses affected with neural tube defects (NTD). The screening characteristics of MSAFP were developed in a large collaborative study in the United Kingdom, published in 1977;[5] shortly thereafter, screening of the pregnant population became increasingly a standard of practice in the United Kingdom. However, due to the fact that in the United States the Food and Drug Administration had no previous experience with screening applications of this nature, and in part due to the opposition of antichoice groups, the first licenses for marketing test kits in the United States were not granted until 1984. In 1986 California initiated its statewide program based on a unique public/private partnership model.

PROGRAM DESCRIPTION

California's program was designed to meet or exceed the guidelines for MSAFP screening published by the American Society of Human Genetics (ASHG) and other professional groups.[6–8] The program was authorized by the State Legislature and implemented by the State Department of Health Services regulations. The patient flow is schematically summarized in Figure 1.

The law requires that all women seen before the 140th day (20th week) of gestation be provided with a state-prepared booklet describing the risks and benefits of MSAFP screening. The woman's signature on the consent/refusal form contained in the booklet indicates whether they choose or decline to participate.

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The Program distributes all forms, tubes, mailing containers, and a provider participation booklet free of charge to all of the almost 7,000 prenatal care providers in California.

Blood specimens are sent to one of eight regionalized private laboratories, under contract with the Program, which conduct the automated assay in accordance with a uniform protocol and under strict quality control of the State Genetic Disease Laboratory. Results are transmitted electronically to the Genetic Disease Branch computer in Berkeley, CA, which interprets them and prints out and mails reports to clinicians.

Screen positive test results and other test results needing some sort of follow-up action are electronically transmitted to 14 state-approved coordinator offices regionally located at area genetic centers. These area genetic centers may be publicly or privately funded, and are under contract with the State to provide follow-up services. Follow-up consists of telephoning the clinician's office, and confirming the patient/pregnancy information used in test interpretation. Coordinators arrange for state-authorized follow-up at 1 of 29 prenatal diagnostic centers (PDC), with 90 satellite sites that meet State criteria for counseling, ultrasound, amniocentesis, karyotyping, and amniotic fluid analysis of AFP and acetylcholinesterase (AChE). The approved centers are reimbursed by the State on an agreed upon fee for service schedule (Table 1).

The original one-time only, all-inclusive participation fee is billed, after testing is complete, to the patient or insurance carrier, but this has been increased over time (Table 2). The $115 fee represents a change to triple marker screening. This increase in fees is an important point because the Program is not a tax-supported service, and the fee may be regarded as a measure of willingness to pay. Despite increases in fees, the participation rate continues to increase.

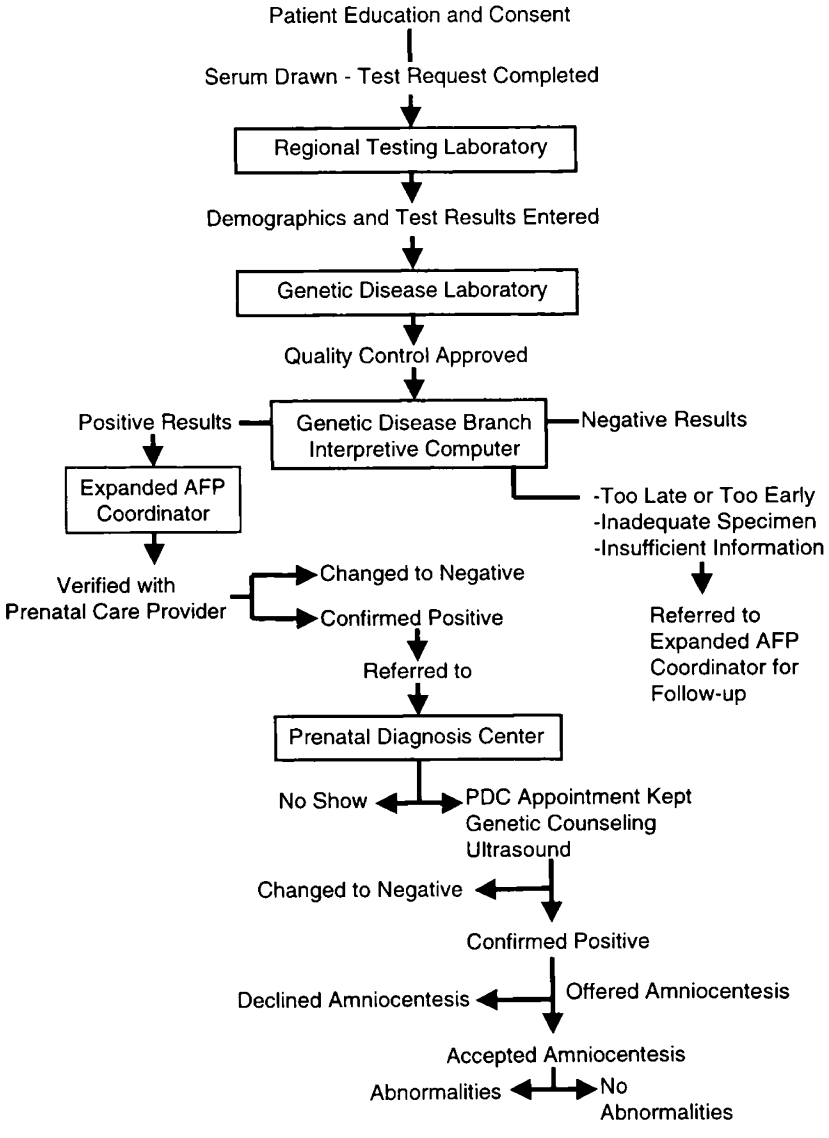

Fig. 1 Patient flow through the screening process in the California Expanded AFP Program.

Table 1
California MSAFP program reimbursements

Genetic counseling	$110.00
Ultrasound	$175.00
Amniocentesis	$125.00
Karyotyping	$385.00
AF-AFP and AF-AChE	$40.00

Table 2
California MSAFP program participation fee

August	1986	$40.00
September	1988	$49.00
October	1991	$53.00
November	1992	$55.00
January	1995	$57.00
July	1995	$115.00
March	1998	$105.00

Utilization of the original MSAFP screening program steadily increased from 41% in 1986 to 63% of eligibles in 1994 (Table 3). From 1986 to 1994, 2,422,881 women elected to participate in this single marker (AFP) screening program, and more than 3,000 birth defects (neural tube defects, abdominal wall defects, and significant chromosome anomalies) were detected. The approved PDCs provided a substantial volume of services during this period, performing 23,463 ultrasounds and 12,634 amniocenteses.

Conversion from single marker to triple marker screening

In mid-1995, the Program implemented triple marker screening. An automated analytical system, AutoDelfia (EG&G Wallac Oy, Turku, Finland); was selected to measure intact human chorionic gonadotropin (hCG), unconjugated estriol (UE_3), and AFP. At the central computer, laboratory assay results are combined with the patient/pregnancy information. The median value for each analyte at each gestational day is determined. The woman's analyte values are then converted to multiples of the analyte median (MoM) for gestational age in days, and adjustments for maternal weight and race are applied. Risks for Down syndrome are calculated using a probabilistic likelihood ratio algorithm[9] based on maternal age and the three analyte MoMs. The Expanded AFP Program is treated as three screening programs. An MSAFP MoM of 2.5 or greater in a singleton pregnancy is screen positive for neural tube or abdominal wall defects (AWD). A term risk of 1:250 or greater, now expressed as a mid-trimester risk of 1:190 or greater) is screen positive for Down syndrome. Screen positive for trisomy 18 initially required values < 0.60 MoM for hCG, < 0.75 MoM for AFP, and < 0.55 MoM for UE_3. The Program now uses a mid-trimester risk of 1:100 or greater as screen positive for trisomy 18, calculated by a probability algorithm similar to the Down syndrome risk algorithm. Blood specimens are accepted if collected between 15 and 20 weeks gestation. Reports of all procedures performed and all diagnoses made are required. Special provisions have been adopted for twins, donated ova, family history of NTD, or exposure to certain teratogenic medications. NTDs and chromosomal disorders, however diagnosed, are classified as reportable disorders under State law.

Expanded AFP Screening Program experience

We report here the experience with the Expanded AFP Screening Program design (in which the Program sets standards and

Table 3
The California MSAFP and expanded AFP program utilization

Year	Program	Number of women eligible[a] to participate in the program	Number of women electing to participate in the program	Percent program utilization
1986	AFP	223,961	91,742	41.0
1987	AFP	467,526	210,369	45.0
1988	AFP	494,295	239,495	48.5
1989	AFP	524,240	262,996	50.2
1990	AFP	563,407	291,459	51.7
1991	AFP	565,392	318,680	56.4
1992	AFP	564,091	335,227	59.4
1993	AFP	550,024	337,295	61.3
1994	AFP	534,783	335,618	62.8
1995	AFP/XAFP	520,879	340,832	65.4
1996	XAFP	511,625	353,828	69.2
1997	XAFP	511,521	356,157	69.6
Total	AFP/XAFP	6,031,743	3,473,698	—

[a] Eligibility: Pregnant women who are in prenatal care between the 15th and the 20th week of gestation.

Table 4
California Expanded AFP 95-97 utilization by age and race

Age group	Hispanic	White	Asian	Black	All Races[a]
34 years and younger	362,050	237,576	60,220	49,584	770,576
35 years and older	27,528	26,769	8,192	4,013	71,929
All ages	391,872	265,642	68,937	53,937	848,083

[a]Includes other and unknown race.

Table 5
California Expanded AFP 95-97 acceptance of amniocentesis

PDC status	Hispanic	White	Asian	Black	All[a]
Appointment kept	19,676	12,931	4,407	3,394	43,073
Confirmed screen positive	12,900 (65.6%)	10,794 (83.5%)	3,503 (79.5%)	2,554 (75.3%)	31,738 (73.7%)
Offered amniocentesis	12,579 (63.9%)	10,611 (82.1%)	3,450 (78.3%)	2,516 (74.1%)	31,102 (72.2%)
Accepted amniocentesis	8,320 (66.1%)	8,046 (75.8%)	2,655 (77.0%)	1,775 (70.5%)	22,188 (71.3%)

[a]Includes other and unknown race.

pays private providers for services in a coordinated statewide system). The period is from July 29, 1995 through December 31, 1997.

Acceptance of the test by pregnant women is voluntary. Women younger than 35 were offered triple marker screening. Women older than 35 were offered either direct referral for amniocentesis or blood testing. A separate consent form was used. There have been no special efforts to promote the Program with mass media or mailings to encourage women to participate in the Program. During the study period there were 1,256,377 eligible pregnancies, and 848,083 or 67.5% of the women elected to participate. Of the 1,082,637 eligible women younger than age 35, 770,576 (71%) participated in screening, and of the 173,740 eligible women older than age 35, 71,929 (41.4%) were participants (Table 4). This reflects the fact that women older than 35 have the option to choose amniocentesis rather than serum screening. Participation by race/ethnicity was reasonably close to representation of the races in the eligible population. Nonparticipation could be due to a failure to offer the test, a cultural lack of understanding of prenatal detection of birth defects, a lack of confidence in a technology that gives only risks, objection to termination of pregnancy, or unwillingness or inability to pay. Limited studies have been performed to characterize this group of nonparticipants.

Of the women who consented to be tested, 96.4% were successfully screened; they received either a screen positive or screen negative test result. Failures occurred due to unsatisfactory specimens or specimens collected too early and never replaced by a satisfactory specimen. All participants were tracked by the

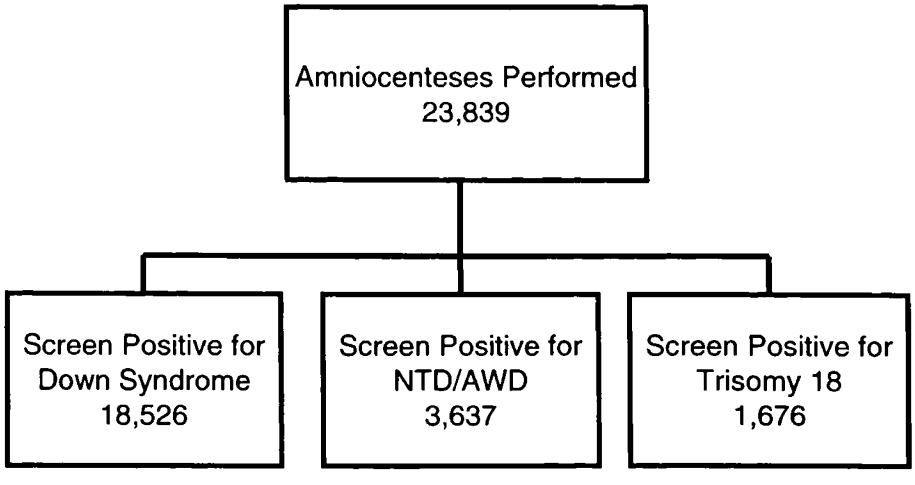

Fig. 2 Amniocenteses performed by indication in the California Expanded AFP Program between 1995 and 1997.

central computer system. Screen positive results or other results needing follow-up were telecommunicated daily to 1 of 14 specially trained regional follow-up coordinator offices under contract with the Program. There were 60,245 or 7.1% initial positive results distributed as follows: 1.5% screen positive for NTD, 5.5% screen positive for Down syndrome, and 0.33% positive for trisomy 18.

Verification of interpretation factors with the prenatal care provider by the coordinators resulted in reclassification of some initial positives to negative, too early or too late for testing. All 47,858 verified screen positives were referred to PDCs for workup. However, 10% declined referral or failed to keep the appointment, and 90% were seen at the PDC. The program provided more than 43,000 genetic counseling services and more than 43,000 ultrasound examinations, and 22,188 women accepted amniocenteses (Table 5). Some women were positive for more than one condition or had more than one procedure, resulting in 23,839 amniocenteses procedures (Fig. 2). As a result of this PDC follow-up, the Program detected 532 NTD, 309 AWD, 570 Down syndrome cases, 133 trisomy 18 cases, and 410 other significant chromosomal defects. One measure of program effectiveness is the number of amniocenteses needed to detect a case. One case of Down syndrome was found for every 33 amniocenteses (570/18,526) and one case of trisomy 18 for every 13 amniocenteses (133/1676). Some NTDs were determined by ultrasound and did not have amniocentesis performed. The ratio was 1 NTD detected for 24 amniocenteses. The overall rate was 23 birth defects per 10,000 women screened (Table 6).

To estimate the detection rate, the program estimated the number of defects expected in the screened population by applying age-specific risk figures for chromosome anomalies and birth prevalence figures for NTD and AWD. This was compared with cases actually found.

For Down syndrome screening, the detection rates were calculated for two age groups: 34 years of age and younger, and 35 years of age and older. Among the younger group of women and the older group of women, 33% and 52% of the expected cases of Down syndrome were detected, respectively. The reported detection rates for Down syndrome, based on a theoretical model that assumes that all screen positive women will complete the entire sequence of tests and procedures, is 51% for women 34 and younger and 85% for women 35 and older (with an overall rate of 62%), with an amniocentesis rate of 5%.[10] In actual practice, in which women can choose to opt out at any point in the offered sequence of diagnostic tests and procedures, the overall program detection rate for Down syndrome was 41%, and the actual amniocentesis rate among women screened was 2.2%. Likewise, detection of NTD at the Program cutoff (2.5 MSAFP MoM for singleton pregnancies) based on a receiver operator curve is theoretically 85% and in practice was 75%.[11]

Table 6
California Expanded AFP 95-97 Program detection rates

	Number expected in screened population	Number detected	Detection rate
Neural tube defect	705	532	75%
Abdominal wall defect	358	309	86%
Down syndrome	1,375	570	41%
Trisomy 18	313	133	42%
Other chromosome		410	
Total		1,954	

BENEFITS EVALUATION

For evaluation purposes and to assess the benefits of the Program, NTD, AWD, and Down syndrome were selected as the major birth defects that the Program was designed to detect and prevent. However, it is clear that there are many additional secondary benefits that were not included in this analysis. Detection of other structural defects, other chromosomal defects, early detection of twins, fetal demise, intrauterine bleeding, improved pregnancy dating, and identification of pregnancies at high risk of fetal and neonatal death and prematurity are also significant benefits. The screening test also is an additional inducement for early prenatal care. An exhaustive cost benefit analysis might want to try to assign a dollar value to these beneficial aspects.

In the determination of the fiscal benefits of the Program, we reviewed the extensive literature on the cost of care for Down syndrome and the meager information on NTD.[12–31] We developed estimates of $450,000 as lifetime costs for Down syndrome and $300,000 for spina bifida. These estimates were used in program planning in 1985. Fortunately, a detailed analysis of the cost of care for birth defects in California, funded by the California Birth Defects Monitoring Program, March of Dimes, and Agency for Health Care Policy Research, was published in the Blue Cross/Blue Shield Association Journal Inquiry.[32] The study looked at incremental costs, i.e., costs over and above those normally associated with the average infant, child, or adult. They included direct medical costs, inpatient/outpatient care, long-term disability, and developmental services and special education. Lost productivity due to mortality and morbidity was included. Calculation of productivity was based on age-related average income for men and women. The authors did not include lost productivity of parents or private out-of-pocket costs such as transportation, home modifications, wheelchairs, and appliances, etc. They did not include family stress-related costs, such as divorce counseling for parents.

This cost of care study produced total lifetime care per case cost avoidance in 1988 dollars at a 5% discount (to adjust for inflation) of $258,000 for spina bifida and $410,000 for Down syndrome. These estimates need to be adjusted to 1996 dollars (Table 7). If cost savings are limited to cases terminated after prenatal detection, the total savings accomplished by the Program through detection of Down syndrome, NTD, and AWD was conservatively estimated as $185,604,684 (Table 7). Because 23% of Down syndrome detected would have been lost due to spontaneous abortion, we only included 77% of terminations in our cost avoidance. Some may argue that, at the current rate of economic growth, a lower discount rate would be a better estimate for a public program. This would increase the cost

Table 7
California Expanded AFP 95-97 cost avoidance

Birth defect	1988 Costs (5% discount rate)		Adjust 1988 $ to 1996 $		Number cases averted		Costs avoided
Spina bifida	$258,000	×	1.338	×	109	=	$37,627,236
Down syndrome	$410,000	×	1.338	×	257[a]	=	$140,985,060
Anencephaly	$5,000	×	1.338	×	224	=	$1,498,560
Gastroschisis	$94,000	×	1.338	×	20	=	$2,515,440
Omphalocele	$159,000	×	1.338	×	14	=	$2,978,388
Total cost avoidance					624		$185,604,684

[a] Corrected for 23% miscarriages.

avoidance figure, which is sensitive to the discount rate. If a discount rate of 2% is used, the cost avoidance would be more than 446 million dollars.

This benefit needs to be compared with the Program costs. Because the State provides all materials and services, except the cost of blood collection, and because all expenditures are accounted for to the State Department of Finance, this provides a unique opportunity to assess the true costs of the Program. Costs such as printing and distribution of forms and educational brochures, videos, postage, information flow and data processing, proficiency testing, quality control, telephoning for follow-up, costs of fee collection, etc., are frequently omitted from the cost estimates of laboratory based screening. The State also operates an NTD registry and a chromosome abnormality registry, pays a pro rata assessment to support the Legislature, and incurs State administrative costs, which are included in the total Program costs.

The Program's expenses from July 1995 to December 1997 were $60,184,903. We estimate that additional expenses to the total health-care system of drawing blood, completing test request forms, and arranging for follow-up incurred by prenatal care providers, was averaged as $10 per woman screened. We include the costs of termination, which was not included in Program expenses, because the abortions at an average cost of $700 would add to Program costs. Thus, the Program's net cost was $69,102,533. The average cost of prevention of one of the listed birth defects was $110,741. The cost benefit rate is $2.69 or more (Table 8). At the 2% discount rate the benefit is $6.45. This is consistent with previous cost benefit analyses of MSAFP published in the literature. This result was achieved in a low prevalence area for NTD. The California Birth Defects Monitoring Program estimates the NTD rate in California as 0.9 per 1000 births and fetal deaths.

Table 8
California Expanded AFP program 95-97 cost–benefit analysis

Program expenses	$60,184,903
Private expenses ($10/test)	$8,480,830
Termination cost ($700/AB)	$436,800
Total cost	$69,102,533
Cost avoidance	$185,604,684
Cost-benefit ratio	$2.69
Cost per birth defect prevented	$110,741
Cost per birth defect detected	$35,365

DISCUSSION

Replacement type analysis was not performed, i.e., the effect of replacing a lost pregnancy with a live birth sometime in the future. The changes would be in the direction of improving the cost benefit ratio, but the adjustment is minor. Some have objected to the application of cost benefit analyses to prenatal screening, arguing that only benefits in health status can be validly accepted as a benefit. They reject the concept of cost avoidance as a result of termination. However, if the objectors accept the current basic political construct in the U.S. that health-care is a commodity that is subject to market forces, they, as prudent buyers, must accept a market-based analysis. Clearly, the maximization of the economic benefits becomes a legitimate objective of any health intervention based upon the market model. On the other hand, if they argue that adequate health-care is a societal benefit and entitlement for all citizens, then there is no basis to restrict access to screening, which is wanted and is used to improve mental health and quality of life of the participants. The cost benefit equation loses much of its significance.

Moreover, if a cost benefit analysis for a screening program that limits the cost avoidance to direct health-care services is performed, the program may not be cost beneficial. In other words, if an HMO or health insurance program pays for screening, it is also paying to avert educational and other costs for which the third party payer for health services is not directly liable.

Tapin et al.,[16] after conducting a cost benefit analysis for the Group Health Cooperative of Puget Sound, concluded:

> "It may be that the time has come to look more closely at cooperative rather than competitive solutions to some health-care problems. Russell has suggested that prevention usually has a price. However, this analysis shows that, in the case of MSAFP screening, the price is paid directly by the insurer, while society receives the net benefit. To the extent that insurers refuse to pay that price and cover screening, participation may drop and society stands to lose. Our conclusions firmly suggest that it would be to the advantage of states and health-care insurers to cooperate in the

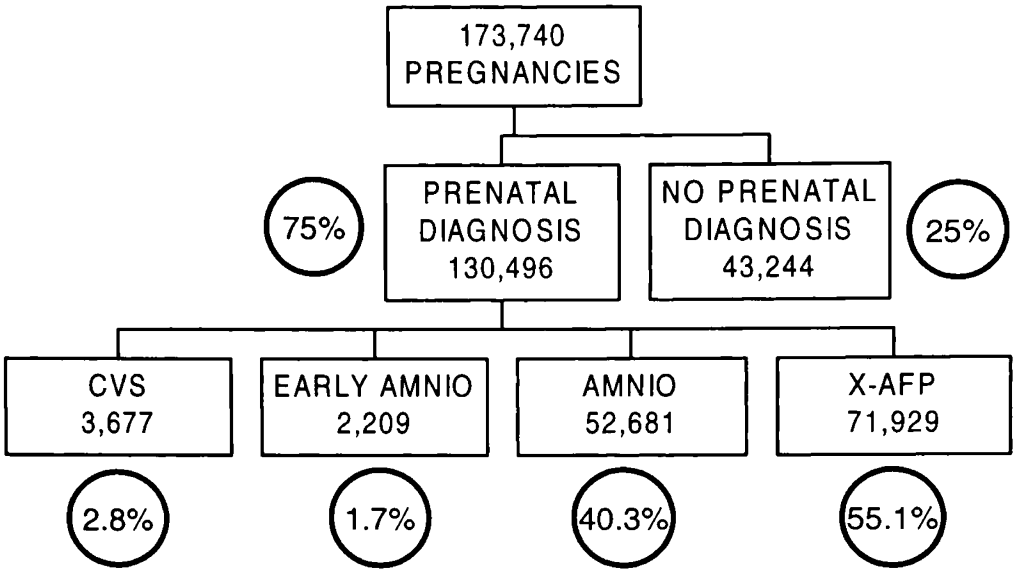

Fig. 3 Testing decisions and outcomes on 173,740 pregnancies in women 35 years and older, 1995–1997.

establishment of programs such as the one undertaken in California. Such cooperation would result in large programs, the economies of scale of which would reduce the two direct costs (the screening test and genetic amniocentesis) that have the greatest effect on the net cost of a screening program. Whether that would result in increased coverage and wider participation remains to be determined."

There has been some discussion about the ultimate effect of serum screening on Down syndrome detection in older women. This is an important consideration due to the increased trend toward older births. Of the 173,740 eligible women 35 and older during the study period, 75% elected to have either prenatal testing or diagnosis and 25% had no test at all (Fig. 3). Of the prenatally tested women, 44.9% elected to have some kind of invasive diagnostic procedure rather than the blood test, and 55.1% elected to have the triple marker test. Based on age-related risk for the 173,740 women, a total of 1,051 Down syndrome births were expected, and 794 or 75.5% were prenatally detected. Based on 515 terminations, after correction for spontaneous losses, we estimate that current prenatal screening practices in California resulted in a 49% reduction in birth prevalence in women older than 35. This is consistent with the estimates of Bishop et al.[33]

It is useful to reflect on the missed opportunities for avoidance of birth defects and the discrepancies of results in actual programs in comparison with the theoretical models or experience with small selective populations. The screening system cannot detect birth defects prenatally among the 5% of women who do not seek care before 20 weeks. This emphasizes the importance of promotion of free or low cost pregnancy testing and early referral for prenatal care. Once in care, the clinician must take the initiative to routinely and universally offer prenatal testing. Without the offer, avoidable cases will occur in the unscreened group. For each woman consenting to be screened, it is important to draw a timely blood specimen, taking appropriate precautions to prevent hemolysis, and get it promptly to the designated screening laboratory for analysis. It is critical to provide the best estimate of gestational age possible and the information needed to apply the adjustment factors. Errors in these steps can lose the window of opportunity to screen. The biology of the markers and the precision and accuracy of the quantitation of analytes are such that a number of affected fetuses do not have results in the screen positive range. Improved markers, improved assays, and modifications of screen positive cutoff levels can help reduce cases missed during screening. Prompt follow-up of screen positive results is important. Although California has 29 PDCs located in population centers and 90 satellite sites, there are still rural areas where access to follow-up is difficult to guarantee. In our program 10% of all high-risk women offered follow-up did not appear for their PDC appointment. These women receive a letter encouraging them to use the "free" follow-up services. Considering the problems of language barriers of our multi-ethnic population, increasingly mobile society, and large numbers of illegal aliens, the fact that only 10% of these high risk women do not complete referral is remarkable. There is, however, a larger group of women who, after counseling and ultrasound scanning, elect not to have an amniocentesis, adding to the population of incompletely screened women. Twenty-five percent of whites and 33% of Hispanics declined amniocentesis (Table 5). Although included in the initial positive rate, they are not included in the final detection rate. Finally, the impact of screening is in part determined by the termination rate. In contrast to reports in the literature of 70-80% termination of Down syndrome, there is a significant number of women in California who elect not to terminate after a diagnosis is made. The overall termination rate of 58.6% for Down syndrome includes ethnocultural differences, because 66% of whites and only 48% of Hispanics elect to terminate

Table 9
California Expanded AFP 95-97 decision for elective termination of pregnancy

	Hispanic		White		Asian		Black		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%
Fetal Abnormality	DX	TAB	DX	TAB	DX	TAB	DX	TAB	DX	TAB
Anencephaly	157	68.2	92	88.0	20	80.0	10	70.0	297	75.4
Spina bifida	74	60.8	69	72.5	7	57.1	6	83.3	162	67.3
All neural tube defects	259	65.3	195	77.4	33	69.7	18	66.7	532	70.7
Gastroschisis	122	8.2	65	10.8	11	18.2	11	0.0	220	9.1
Omphalocele	19	26.3	16	18.8	2	50.0	3	33.3	45	31.1
All abdominal wall defects	164	18.9	95	21.1	17	35.3	15	13.3	309	21.4
Down syndrome	244	47.5	196	65.8	72	70.8	24	62.5	570	58.6
Trisomy 18	56	55.4	45	73.3	16	68.8	6	50.0	133	66.2
All chromosome abnormalities	443	44.7	401	56.1	138	57.2	60	40.0	1113	51.0
All abnormalities	866	46.1	691	57.6	188	57.4	93	40.9	1954	51.8

DX, prenatally detected; TAB, therapeutic abortion.

(Table 9). All of our cases received face-to-face counseling with a board certified counselor.

The case for state-administered screening has been stated. We hope you will agree that this model has achieved its overall objectives of providing universal access to low cost, high quality screening and follow-up.

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