ORIGINAL ARTICLE

Integrated and first trimester prenatal screening in California: program implementation and patient choice for follow-up services

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ABSTRACT

Objectives The California Prenatal Screening Program serves over 350 000 women annually. This study examines utilization rates for the various screening options and patient choices regarding follow-up services.

Methods The study tracked patients with first trimester positive results for Down syndrome to examine patient decisions regarding follow-up services and/or additional screening and to identify determinants of patient decisions. For first trimester screen positive women who elected further screening, second trimester integrated screening results were analyzed. The Genetic Disease Screening Program Chromosome Registry was used to identify Down syndrome cases.

Results Ethnicity, but not age, was a strong predictor of acceptance of prenatal diagnosis. Approximately 47% of first trimester screen positive women opted for further screening. Among these women, 46% percent received an integrated screen negative result. All but one confirmed Down syndrome case in this cohort were still screen positive.

Conclusions Data from the California Prenatal Screening Program indicate that all of the major screening modalities continue to be utilized. The wide range of choices made by women with screen positive results demonstrate the importance of including multiple options within the Program. Providing integrated screening to first trimester Down syndrome screen positive women reduced the number of unnecessary invasive procedures. © 2012 John Wiley & Sons, Ltd.

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Supporting information may be found in the online version of this article.

INTRODUCTION

The California Department of Public Health, Genetic Disease Screening Program has been offering prenatal screening to pregnant women in California since 1986. With more than 350 000 pregnant women participating in prenatal screening each year, the California Prenatal Screening Program (the Program) is one of the largest in the world. It is also one of a few screening programs to include the offer of diagnostic follow-up for screen positive women and to track the outcomes of pregnancies in the screened population.

Beginning in April 2009, the Program incorporated first trimester biochemical analytes and nuchal translucency (NT) ultrasound measurements into the risk assessments for Down syndrome and Trisomy 18. This has resulted in several new patient options for prenatal screening, depending on patient choice, the gestational age at the initiation of prenatal care, and the availability of NT ultrasound. In this paper, we describe the screening modalities available to California women, along with Program utilization rates across the large and diverse California population. We then track first trimester screen positive patients through follow-up, look at determinants of patient choices at each decision point, and examine the results of risk recalculation in the second trimester following a first trimester positive screening result.

PROGRAM DESCRIPTION

Screening is implemented in obstetrical offices and clinics when licensed medical professionals order the blood test for patients who have consented to screening. Blood specimens along with test request forms containing patient information are submitted to Program laboratories for processing. First trimester specimens are analyzed for pregnancy-associated plasma protein-A and total chorionic gonadotrophin (Perkin-Elmer Life Sciences, Waltham, MA). Second trimester specimens are analyzed for alpha-fetoprotein, total chorionic gonadotrophin, unconjugated estriol (Perkin-Elmer Life Sciences, Waltham, MA) and dimeric inhibin-A (Applied Biosystems, Brea, CA).[1] Each analyte value is compared with the median analyte value for the gestational age to produce a multiple of the median (MoM). The MoMs are then adjusted for patient weight and maternal race/ethnicity. Further adjustment factors are applied for diabetic women and women who smoke cigarettes. Analyte MoMs, along with nuchal

translucency data, if available, are used to produce a risk estimate and the screening result.

As shown in Table 1, there are a variety of combinations of data that result in different screening modalities: First Trimester Combined (F) when there is a first trimester specimen and NT data; Sequential Integrated (I) when the First Trimester Combined result is modified by data from a second trimester specimen; Serum Integrated (S) when there are both first and second trimester specimens, but no NT measurement; Quad marker screening (Q) when there is only a second trimester specimen; and Quad marker with NT (T) when there is an NT result with a second trimester specimen. The term 'Sequential Screening' has previously been applied to a modality that offers second trimester screening only to patients with first trimester negative results.[2] When women with very low first trimester risk are excluded from further screening, it is called 'Contingent Screening'. Alternatively, when no first trimester risk assessment is provided, it is called 'Integrated Screening'. None of these modalities describes the California Program. Therefore, the term 'Sequential Integrated' was adopted to reflect the hybrid nature of our Program. First trimester results are made available so that women may make decisions earlier in pregnancy; integrated screening is offered to all patients, regardless of first trimester results.

Program data on Sequential Integrated results include a significant fraction of patients with first trimester positive results who chose second trimester screening instead of immediate diagnosis. Table 2 presents Program utilization rates for one full year, starting October 2009. (Because the Program was implemented incrementally, the first six months of the Program are not fully representative of Program utilization and were thereby excluded from this analysis.) Overall, 60% of screening patients accessed either Serum Integrated or Sequential Integrated screening. Although utilization of integrated screening differed by ethnicity, more than half of patients in each ethnic category received either Sequential Integrated or Serum Integrated screening results. Conversely, in all ethnic categories, a significant percentage of screening patients continued to utilize Quad marker screening.

As shown in Table 2, utilization of screening types differed by age group; women under the age of 30 more often obtained Quad marker screening while women over 30 participated more frequently in integrated screening. This in part reflects the interaction between race and age within the Program. Black and Hispanic participants overall were younger than the Asian and non-Hispanic White participants in this data set.

All modalities include results for Down syndrome and Trisomy 18 screening. Risk assessment is based on the standard multivariate Gaussian algorithm[3,4] with the parameters for Down syndrome risk assessment from the Serum Urine and Ultrasound Screening Study (SURUSS)[5] and the parameters for Trisomy 18 risk assessment from other studies.[6–8] When a second trimester specimen is available, screening results for neural tube defects (NTD) and Smith–Lemli–Opitz syndrome are also provided.[9]

If results are screen positive, the patient is offered a referral to a State-approved Prenatal Diagnostic Center (PDC) for follow-up services provided by the Program.[10] First trimester screen positive patients are offered genetic counseling and chorionic villus sampling (CVS) for diagnosis of chromosome defects; these patients may also choose second trimester diagnosis or screening. Second trimester screen positive patients are offered genetic counseling, a detailed ultrasound survey, and amniocentesis for diagnosis. Throughout this paper, 'diagnosis' refers to diagnosis of chromosomal abnormalities by either CVS or amniocentesis. All PDC services, including genetic counseling, invasive diagnostic testing, and the anatomic survey comply with Program standards; anatomical surveys are conducted in accordance with standards set forth by the American Institute of Ultrasound in Medicine.[11] A more detailed description of the Program is available in the supporting information.

MATERIALS AND METHODS

All data related to screening, including analytical results, patient demographic data, and patient decisions regarding follow-up care are stored in an SQL database (Microsoft Corp., Redmond, WA). This tracking system allows the Program to appropriately guide screen positive women through follow-up care and to analyze patterns in decision making among the screen positive population. The Program database also includes records from the Genetic Disease Screening Program Chromosome Registry (the Registry); the Registry was used to identify affected pregnancies (screen positive, screen negative, and unscreened) for this paper. Analysis for this study was performed using SAS 9.1 for Windows® (SAS Institute, Inc., Cary, NC).

Table 1 **Elements and cutoffs of screening modalities**

	Components			Cutoffs			
Screening modality	1st T Serum	NT	2nd T Serum	Down Syndrome (Risk)	Trisomy 18 (Risk)	NTD (Alpha-fetoprotein MoM)	SLOS (Risk)
First Trimester Combined (F)	•	•		1 : 100	1 : 50	—	—
Sequential Integrated (I)	•	•	•	1 : 200	1 : 100	2.5	1 : 100
Serum Integrated (S)	•		•	1 : 200	1 : 100	2.5	1 : 100
Quad (Q)			•	1 : 150	1 : 100	2.5	1 : 100
Quad + NT (T)		•	•	1 : 200	1 : 100	2.5	1 : 100

Bullet points (•) indicate which elements are included in the screening modalities: first trimester serum (1st T Serum), nuchal translucency (NT), second trimester serum (2nd T Serum). Cutoffs for each of the screening tests are given. First trimester combined screening does not include assessment for NTD or SLOS.

Table 2 Summary of program utilization: number of pregnancies by screening type, maternal age at term, and ethnic group

		F	I	S	Q	T
Maternal age (completed years)						
	<20	604	4527	7648	14514	231
		(2%)	(16%)	(28%)	(53%)	(1%)
	20–24	1923	15481	20430	33360	662
		(3%)	(22%)	(28%)	(46%)	(1%)
	25–29	2778	29078	27466	35430	886
		(3%)	(30%)	(29%)	(37%)	(1%)
	30–34	3096	40199	25035	27529	889
		(3%)	(42%)	(26%)	(28%)	(1%)
	35–39	3650	25668	9433	12043	613
		(7%)	(50%)	(18%)	(23%)	(1%)
	40–44	1497	5350	1906	2711	152
		(13%)	(46%)	(16%)	(23%)	(1%)
	45–49	89	336	99	157	15
		(13%)	(48%)	(14%)	(23%)	(2%)
	50+	7	24	5	15	0
		(14%)	(47%)	(10%)	(29%)	(0%)
	Total cases	13644	120663	92022	125759	3448
		(4%)	(34%)	(26%)	(35%)	(1%)
Ethnicity						
	Hispanic	4836	47767	54725	75179	1780
		(3%)	(26%)	(30%)	(41%)	(1%)
	White	5019	38563	17487	24801	905
		(6%)	(44%)	(20%)	(29%)	(1%)
	Asian	1645	17039	8475	9273	302
		(4%)	(46%)	(23%)	(25%)	(1%)
	Black	797	5100	4990	8530	206
		(4%)	(26%)	(25%)	(43%)	(1%)
	Other	833	7831	4140	5340	162
		(5%)	(43%)	(23%)	(29%)	(1%)
	Multiple	514	4363	2205	2636	93
		(5%)	(44%)	(22%)	(27%)	(1%)
	Total cases	13644	120663	92022	125759	3448
		(4%)	(34%)	(26%)	(35%)	(1%)

The First Trimester Screening (F) category includes only women who did not continue on for second trimester screening. Women who obtained a first trimester screening result followed by a sequential integrated results are included in the I category. Other screening modalities are: Serum Integrated (S), Quad (Q) and Quad + NT (T). The Program collects detailed race/ethnicity data from all screening patients. For the purposes of this study, data were grouped into six broader categories: Hispanic; Non-Hispanic White; Asian (Japanese, Chinese, Korean, Filipino, Vietnamese, Cambodian, Laotian, and Other Southeast Asian); Black; Other (Native American, Middle Eastern, Asian Indian, Hawaiian, Guamanian, Samoan, and unspecified); and Multiple (patients with more than one race/ethnicity selected, with the exception that patients who selected both Hispanic and White were categorized as Hispanic).

For this analysis, we track first trimester screen positive patients through follow-up. We look at patient choices at each decision point: to go to the PDC for genetic counseling, to have an invasive diagnostic procedure, or to have Sequential Integrated screening. We examine potential predictors of these decisions such as patient demographic descriptors (age and ethnicity), the numeric risk for Down syndrome screening, an additional positive result for Trisomy 18 screening, and ultrasound findings (in the case of amniocentesis). Finally, we present preliminary data on the recalculation of risk when a second trimester specimen is added to a first trimester positive result.

SCREEN POSITIVE RATE

Table 3 presents the screen positive rate for Down syndrome and Trisomy 18 screening for the different screening modalities along with the median age of participants for each modality.

Table 3 **Program utilization, screen positive rates, and procedures per chromosomal abnormality (October 2009–September 2010)**

	Total # cases	Median patient age at term	Screen positive	Screen negative	Positive rate	# Diagnostic procedures	# Down syndrome cases	# Trisomy 18, 13, and Turner cases	# Procedures/ Down syndrome	# Procedures/ Chromosomal abnormality
F	13644	32.5	2274	11370		1763	164	81	10.75	7.20
I	120663	31.4	3940	116723	3.3%	1983	99	36	20.03	14.69
S	92022	28.4	3514	88508	3.8%	1475	66	41	22.35	13.79
Q	125759	27.1	5157	120602	4.1%	2084	99	47	21.05	14.27
T	3448	29.7	176	3272	5.1%	72	2	2	36.00	18.00

Total numbers of pregnancies screened, median patient age at term, and screen positive rates for Down syndrome and Trisomy 18 are given for each screening modality. Cases positive only for NTD or SLOS are not included as Screen Positive cases. Number of diagnostic procedures, number of Down syndrome cases, number of Trisomy 18, Trisomy 13, and Turner syndrome cases identified, and the number of procedures per Down syndrome case and the number of procedures per chromosomal abnormalities identified (including Down syndrome, Trisomy 18, Trisomy 13, and Turner syndrome) are listed. 'F' or First Trimester Combined Screening cases includes cases for which only first trimester screening was provided. This does not include women who went on to obtain sequential integrated screening. Because most First Trimester screen negative women go on for sequential screening, the positive rate for the 'F' category is not meaningful.

Positive rates are strongly influenced by the age distribution in the population. Table 3 also includes the number of Down syndrome, Trisomy 18, Trisomy 13, and Turner syndrome cases diagnosed through follow-up at a PDC. As shown, the number of procedures per case detected is lower after first trimester screening. This may be due to two factors. First, because the cutoff for first trimester screening is lower than for second trimester screening, the group of pregnancies considered screen positive after the first trimester have a higher average risk than the second trimester screen positive group. Second, as described below, there is an association between the first trimester numerical risk and patient acceptance of prenatal diagnostic testing.

As shown in Table 4, 134307 women obtained a First Trimester Combined risk assessment. Approximately 3.2% ($n=4267$) were screen positive. Cases were excluded from further analysis if they fell into two categories: pregnancies that resulted from ovum donation or for which the ovum-donor status is unknown ($n=282$), and pregnancies that were screen positive for Trisomy 18 only ($n=69$). The remaining study population, pregnancies with a positive screening result for Down syndrome (first trimester positive Down syndrome, FPOS), included 3916 cases. Twin pregnancies ($n=67$) were excluded from the analysis of the effect of risk on decision-making. Risk distribution over each age group was fairly uniform. The age distribution in the FPOS population was similar in the four major ethnic groups.

The decision to accept referral to a Prenatal Diagnostic Center

Figure 1 outlines the decision pathway for FPOS patients. All women with a first trimester positive screening result are offered a referral to a PDC for genetic counseling, followed by the option of obtaining CVS or amniocentesis or undergoing second trimester screening. The first decision is whether or not to accept the referral to a PDC. The overall rate of acceptance of PDC referral and genetic counseling for FPOS women was 79% ($n=3093$, including 44 twin pregnancies). A logistic regression model for acceptance of referral was created including age, ethnicity, risk group, and the additional screening status for Trisomy 18. Models including interaction

Table 4 **Recalculation of first trimester screening results by sequential integrated screening**

	First trimester negative	First trimester positive
First trimester	130040	4267
	(96.8%)	(3.2%)
Second trimester		
No further screening	11370	2274
	(8.7%)	(53.3%)
Integrated screening	118670	1993
	(91.3%)	(46.7%)
Integrated negative	115052	920
Integrated positive	3618	1073

Patients are classified by their second trimester screening results after both first trimester screen negative and first trimester screen positive results.

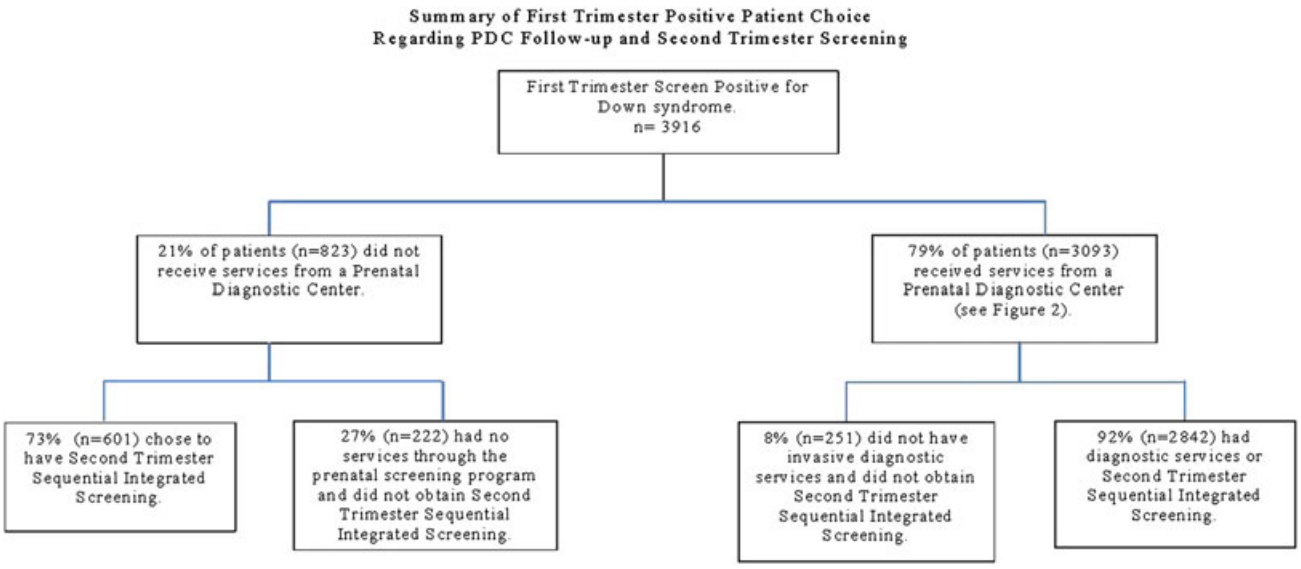

Figure 1 **The decision flow of patients not having follow-up services other than genetic counseling at PDC**

terms were created, but did not improve the fit. After backward selection, few predictors remained significant. Results of the model are summarized in Table 5. Modeled as log-transformed odds, risk was a significant predictor of acceptance of referral. Age was included in the model in both linear and quadratic terms; acceptance of PDC referral does not appear to be significantly associated with maternal age. Compared with the other ethnic groups, Asians and Hispanics had a higher acceptance rate of referral (81%). A screen positive result for Trisomy 18 screening in addition to the positive result for

Table 5 **Acceptance of referral to prenatal diagnostic centers and diagnostic testing**

		Population	Referred	Diagnostic procedure	Referral		DX Procedure	
					coefficient	95% CI	Coefficient	95% CI
Continuous variables								
	Intercept				1.9068		0.8174	
	Log(Odds)	3849	3049	1751	0.1279 *	(0.0566,0.1992)	0.1989 *	(0.1321,0.2657)
	Age	3849	3049	1751	0.0202	(−0.1227,0.1631)	0.0751	(−0.0552,0.2054)
	Age^2	3849	3049	1751	−0.0007	(−0.0028,0.0013)	−0.0013	(−0.0032,0.0006)
					OR	95% CI	OR	95% CI
Race/Ethnicity								
	White	1248	958	689	Ref		Ref	
	Hispanic	1249	1010	352	1.223 *	(1.006,1.487)	0.201 *	(0.165,0.245)
	Asian	879	712	464	1.296 *	(1.046,1.606)	0.734 *	(0.595,0.906)
	Black	130	95	55	0.800	(0.530,1.209)	0.551 *	(0.356,0.852)
	Other	197	153	106	1.015	(0.707,1.457)	0.871	(0.599,1.265)
	Multiple	146	121	85	1.456	(0.927,2.288)	0.925	(0.609,1.403
T18 Screening								
	Negative	3629	2861	1626	Ref		Ref	
	Positive	220	188	125	1.155	(0.747,1.785)	0.953	(0.645,1.409)

Data and modeling results for decision to accept referral to a Prenatal Diagnostic Center (singleton pregnancies only) and diagnostic testing. The numbers and percentages are from univariate analysis of the individual variables. Risk is modeled on a log-linear basis. Age is modeled both linearly and quadratically. Categorical variables are compared with reference (ref.) categories: Non-Hispanic White women, in the case of race, and screen negative women, in the case of Trisomy 18 screening results. The assessment of significance is from the logistic regression model incorporating all these variables and adjusting rates accordingly.

Down syndrome screening was not a significant predictor of referral acceptance. Most of the women with double positive results were in the highest risk strata for Down syndrome and had the correspondingly highest rates of acceptance of PDC referral.

The decision to have prenatal diagnosis

For women who go to the PDC for counseling, the next decision point offers complex choices (see Figure 2). A woman must decide whether or not to undergo invasive diagnostic testing, and if she does, whether to obtain CVS or amniocentesis. Moreover, if a woman decides to wait for amniocentesis, she has the option of a detailed ultrasound anatomy survey before the amniocentesis.

Of the women who were seen at a PDC ($n=3093$), 57% had prenatal diagnosis ($n=1777$). Although the FPOS result is available in the first trimester, more of the women who chose an invasive procedure had amniocentesis ($n=999$) compared with CVS ($n=789$). Eleven women had both CVS and amniocentesis.

The analysis of the decision regarding diagnosis was performed on the group of singleton pregnancies seen at a PDC ($n=3049$). The baseline predictors in the logistic regression model for acceptance of prenatal diagnosis were the same as the model for acceptance of referral. Backward selection produced a similar set of significant predictors. Results of the model are summarized in Table 5.

On the basis of the log-linear model, risk was a significant predictor of acceptance of diagnostic testing. Risk was also examined as a categorical variable to determine if there was a risk threshold at which the median rate of acceptance of diagnostic testing would drop off. We found that the acceptance rate for women with risk greater than 1 : 45 was fairly constant at approximately 60%, while women with risks between 1 : 45 and 1 : 105 accepted diagnostic testing at a rate approximately 10% lower.

Ethnicity was a strong predictor; only 35% of Hispanic, 57% of Black, and 66% of Asian women opted for an invasive diagnostic procedure compared with 72% of non-Hispanic White women. Maternal age was not a significant predictor of this decision. As for PDC referral, an additional positive screening result for Trisomy 18 was not a significant predictor of the decision.

Of the 999 women who had amniocentesis, 93% ($n=925$) had a preceding ultrasound anatomy survey. Conversely, of the 1238 women who had an ultrasound anatomy survey and for whom an amniocentesis was indicated, 74% elected amniocentesis. Notably, the acceptance rate of amniocentesis did not depend on whether the anatomy survey was normal ($n=1026$; 83%) or abnormal ($n=212$; 17%); following ultrasound, the subsequent rate of amniocentesis acceptance was 74% within both normal and abnormal groups. Within the group of women who had an ultrasound, 55% of the Down syndrome cases (50 of 91) had no abnormal findings on ultrasound.

Patients who declined prenatal diagnosis

The majority of FPOS women who did not opt for prenatal diagnosis went on to have further screening. Among the women who accepted a PDC referral but declined diagnostic testing at the PDC ($n=1316$), 81% had Sequential Integrated screening ($n=1065$). Among the women who declined PDC referral ($n=823$), 73% had Sequential Integrated screening ($n=601$). Only 27% did not return for further screening ($n=222$).

In addition, there were 147 women who had only genetic counseling as part of their PDC referral and accepted neither prenatal diagnosis nor Sequential Integrated screening and 106 women who had a second trimester ultrasound, but no diagnosis or further screening. Among the group of women who did not have further services ($n=475$), 91 pregnancies were lost or terminated, 61 women had diagnostic services

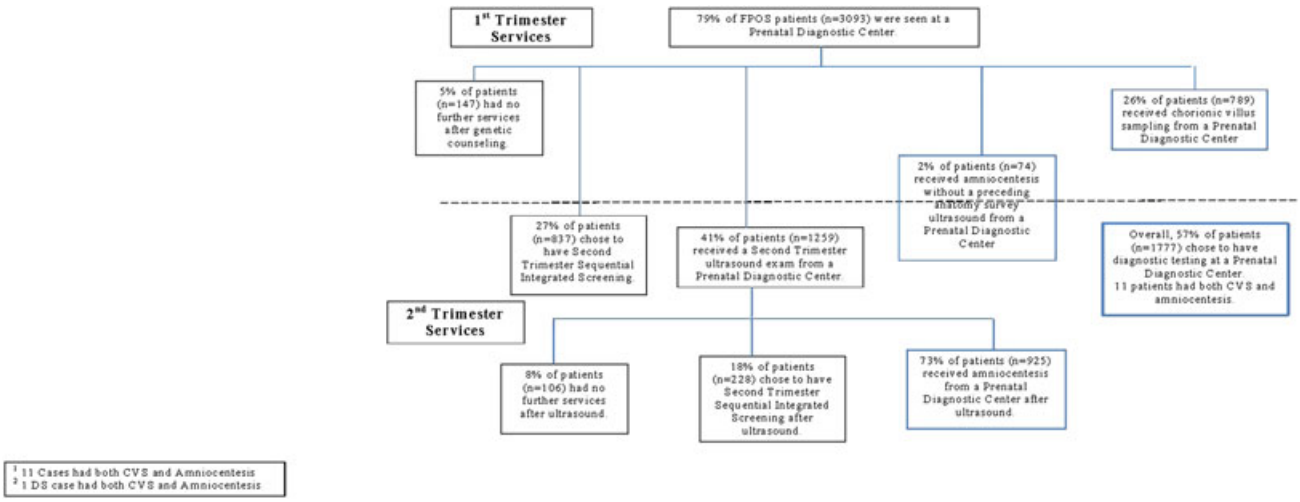

Figure 2 Patient flow after follow-up services at prenatal diagnostic centers for FPOS screening. Numbers and percentages of patients at each decision point. Numbers in the flow chart do not necessarily sum to the number in the proceeding box because, as a result of special circumstances, 13 patients had both CVS and a second trimester service (either ultrasound or amniocentesis)

outside the California Program, 53 women were recorded as declining all services, and 63 women stated an intention to receive Sequential Integrated screening but did not.

Results of recalculation

As shown in Table 4, 47% of first trimester positive women went on to submit a second trimester specimen and obtain Sequential Integrated screening ($n = 1993$). Of these, 1073 (54%) remained screen positive while 920 (46%) recalculated to screen negative. Down syndrome cases among the screened population were identified based on birth outcome forms and records submitted to the Registry. Among the FPOS population ($n = 4267$), there were 296 Down syndrome cases, 189 of which were identified through prenatal diagnostic testing. Among unaffected pregnancies, approximately 48% (806/1662) recalculated to screen negative in the second trimester, significantly reducing the indication for invasive diagnostic testing. Among affected pregnancies, only 1 of 90 Down syndrome pregnancies recalculated to screen negative.

CONCLUSION

The California Prenatal Screening Program was designed to accommodate a large and diverse population and a range of patient choices. Overall, 60% of prenatal screening cases, including more than half of screened women in each ethnic category, obtained either Serum Integrated or Sequential Integrated screening. Of patients screened, 38% obtained a First Trimester Combined risk assessment, making information available earlier in pregnancy. The continuing utilization of all of the major screening options demonstrated that in California, one screening modality does not fit all. Identification of these utilization patterns contributes to Program assessment and Program development.

For patients with screen positive results, the California Program offers referral to State-approved Prenatal Diagnostic Centers for follow-up services at no additional cost to individuals. This study documents the wide range of choices made by women whose first trimester screening results were positive for Down syndrome. The data indicate that women with first trimester screen positive results follow many different decision pathways, utilizing the wide-ranging options offered by the Program.

Recalculation results show that providing second trimester screening to screen positive women can reduce the number of unnecessary invasive procedures; 48% of unaffected pregnancies were screen negative in the second trimester following a first trimester screen positive result. Only 1 of 90 Down syndrome pregnancies recalculated to screen negative with a second trimester screen. Further analysis of this data is needed to better understand the implications for all first trimester positive women.

The goal of the California Prenatal Screening Program is to provide appropriate options for our diverse population. For a given patient, the best possible screening modality depends on when that individual accesses prenatal screening and whether or not she obtains a nuchal translucency ultrasound. For screen positive patients, the decision of whether to pursue follow-up services or further screening is complex and individual. The inclusion of multiple screening options and a wide range of patient choices for follow-up have been key to the Program's success as a statewide Public Health Program.

WHAT'S ALREADY KNOWN ABOUT THIS TOPIC?

- Sequential screening improves detection of Down syndrome in First Trimester Combined screen negative patients.

WHAT DOES THIS STUDY ADD?

- California offers multiple options for prenatal screening and follow-up.
- Women with first trimester screen positive results follow many different decision pathways. Half of them choose additional screening rather than invasive diagnostic procedures.
- Ethnicity, but not age, is a strong predictor of acceptance of invasive diagnostic procedures.

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