

OBSTETRICS

Trends in state/population-based Down syndrome screening and invasive prenatal testing with the introduction of first-trimester combined Down syndrome screening, South Australia, 1995-2005

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OBJECTIVE: The purpose of this study was to review trends in the use of maternal serum Down syndrome screening and invasive prenatal testing before and after the introduction of a state-based first-trimester combined Down syndrome screening program.

STUDY DESIGN: A retrospective population-based study was performed on first- and second-trimester Down syndrome screening, invasive prenatal testing, and prenatal detection of Down syndrome from 1995 to 2005 in South Australia with data from state-based registers. Chi-square tests were used to evaluate trends.

RESULTS: There was a significant decrease in the use of second-trimester Down syndrome maternal serum screening (from 75% in 1995 to 25% in 2005; $P < .001$) and a corresponding significant increase in first-trimester combined screening (from 0.8% in 2000 to 49% in

2005; $P < .001$). The proportion of all confinements that involved invasive prenatal testing fell (from 9.3% in 1995 to 7.6% in 2005; $P < .001$). There was a significant decrease in the number of invasive prenatal tests that were needed to detect 1 Down syndrome fetus (from 86 tests in 1995 to 40 tests in 2005; $P < .001$), with no significant change in the proportion of Down syndrome cases that were detected prenatally.

CONCLUSION: The introduction and increased use of first-trimester combined Down syndrome screening has been associated with more efficient use of invasive prenatal testing in South Australia and has maintained a high level of overall prenatal detection.

Key words: Down syndrome, screening, first-trimester combined screening, prenatal diagnosis, aneuploidy

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★ EDITORS' CHOICE ★

First-trimester nuchal translucency was developed as a screening modality for Down syndrome in the early 1990s by Nicolaides et al.¹ Combined first-trimester Down syndrome screening, which provides risk estimates based on nuchal translucency, maternal serum analytes, and maternal age, has resulted in Down syndrome detection rates that range from 79% to 90%, with a false positive rate of 5%.²⁻⁵

Invasive prenatal tests such as amniocentesis and chorionic villus sampling (CVS), although diagnostic for Down syndrome, are associated with a small risk of miscarriage. The goal of any Down syndrome screening method is to maximize detection and to minimize the risk. This can be achieved by the reduction of the screening false-positive rate, thereby the reduction of the number of

women who would be offered invasive prenatal testing. Indeed, second-trimester Down syndrome screening has been shown to achieve this by reducing the number of invasive prenatal tests without lessening detection rates, specifically in women who are ≥ 35 years old.⁶ First-trimester combined Down syndrome screening should provide similar, if not more, benefit to those women who are seen earlier with second-trimester screening. This would be particularly important as the average age of the gravid population increases.⁷

Large research trials have documented the improved performance of first-trimester combined Down syndrome screening compared with second-trimester maternal serum screening.⁸ Consequently, first-trimester Down syndrome screening is being introduced into many communities internationally. When applied in a community setting,

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however, first-trimester combined Down syndrome screening may differ in clinical outcomes, such as the use of screening and prenatal testing, from single institutions or research trials.

A state-based first-trimester combined Down syndrome screening program was introduced in South Australia in 2000. It was offered in parallel with the existing program of second-trimester maternal serum screening and screening that was based on maternal age with CVS or amniocentesis. The aim of our study was to review trends in the use of first-trimester combined screening, second-trimester maternal serum screening, and invasive prenatal testing (CVS and amniocentesis) and to record any alterations in the overall prenatal detection of Down syndrome cases before and after the introduction of a state-based first-trimester combined Down syndrome screening program.

MATERIAL AND METHODS

A retrospective population-based study was performed for the years 1995-2005 on the use of Down syndrome screening and invasive prenatal testing in South Australia with data from the South Australian Birth Defects Register and the Department of Genetic Medicine at the Women's and Children's Hospital. Comprehensive annual audits are maintained with ethics approval from the Women's and Children's Hospital Research Ethics Committee and under the provisions of Section 64d of the South Australian Health Commission Act.

South Australia is a state that encompasses approximately 1 million square kilometers and that has 1.54 million inhabitants with approximately 18,000 births per year. Most South Australians live in the capital city of Adelaide (population approximately 1 million), with the remaining residents residing in rural and remote communities. The databases that were accessed to ascertain outcomes from South Australia were from (1) the South Australian Maternal Serum Antenatal Screening (SAMSAS) Program, Department of Genetic Medicine, Women's and Children's Hospital; (2) the South Australian State Neonatal Screen-

ing Program; (3) the Department of Cytogenetics, Department of Genetic Medicine, Women's and Children's Hospital; (4) the South Australian Birth Defects Register, Department of Genetic Medicine, Women's and Children's Hospital; and (5) South Australian Perinatal and Abortion Statistics, Department of Health. These combinations of databases have been shown to achieve a high level of ascertainment in fetal and neonatal karyotypes for the state of South Australia.⁹

In South Australia, all births of at least 20 weeks gestation or 400-g birthweight and all terminations of pregnancy at any gestation are required to be reported, according to the legislation on specified forms, to the Pregnancy Outcome Unit of the Department of Health. Birth defects are included in the perinatal notifications. For terminations of pregnancy, the grounds for the termination have to be specified so that terminations for birth defects can be ascertained. All data on birth defects from these notifications are collated by the South Australian Birth Defects Register, which adds cases that are diagnosed after discharge from the hospital up to the child's fifth birthday (also notified under legislation). The Pregnancy Outcome Unit communicates with providers to ascertain the screening modalities and diagnostic tests that were performed prenatally for all Down syndrome cases.¹⁰

Antenatal screening methods for Down syndrome detection that were used in South Australia during this time period were second-trimester maternal serum screening, first-trimester combined screening (introduced in 2000), and morphologic ultrasound screening followed by diagnostic test (CVS or amniocentesis) or a diagnostic test that was based on advanced maternal age alone. Diagnostic testing methods that were used were CVS or amniocentesis that was performed after the aforementioned screening tests or based on patient choice. The use of antenatal ultrasound evaluation for all confinements remained high over this time period, approximately 97%.¹⁰

Second-trimester maternal serum Down syndrome screening was intro-

duced in South Australia in 1991 and has been performed in 2 laboratories. SAMSAS performed over 90% of second-trimester maternal serum screenings in South Australia. The maternal serum markers included were serum alpha-fetoprotein (MSAFP), free α subunit of human chorionic gonadotrophin, free β subunit of human chorionic gonadotropin, and unconjugated estradiol.¹¹ From June 2001, the use of free α human chorionic gonadotrophin was discontinued as 1 of the serum markers.

State-based first-trimester combined Down syndrome screening was introduced in South Australia in 2000. All first-trimester maternal serum analyte measurements were performed at SAMSAS. First-trimester maternal serum analytes included free β human chorionic gonadotrophin and pregnancy-associated plasma protein-A. Nuchal translucency measurements were performed at 10 ultrasound practices in South Australia. Each ultrasound site has sonographers who are trained in nuchal translucency measurement according to Fetal Medicine Foundation Guidelines¹² and are accredited by the Royal Australian and New Zealand College of Obstetricians and Gynaecologists; program performance is monitored by the SAMSAS-run Nuchal Translucency Quality Assurance Program.

The SAMSAS laboratory showed an increasing trend of screen-positive maternal serum screening results in the later half of the 1990s from 4.6% in 1995 to 7.1% in 2000. As the result of this trend and the introduction of first-trimester combined Down syndrome screening based on the Fetal Medicine Foundation Guidelines, risk cut off values were changed from 1 in 405 before the introduction of first-trimester combined Down syndrome screening to 1 in 300 thereafter. Valid risk reports were issued after adjustment for confirmed gestational age and multiple pregnancies.

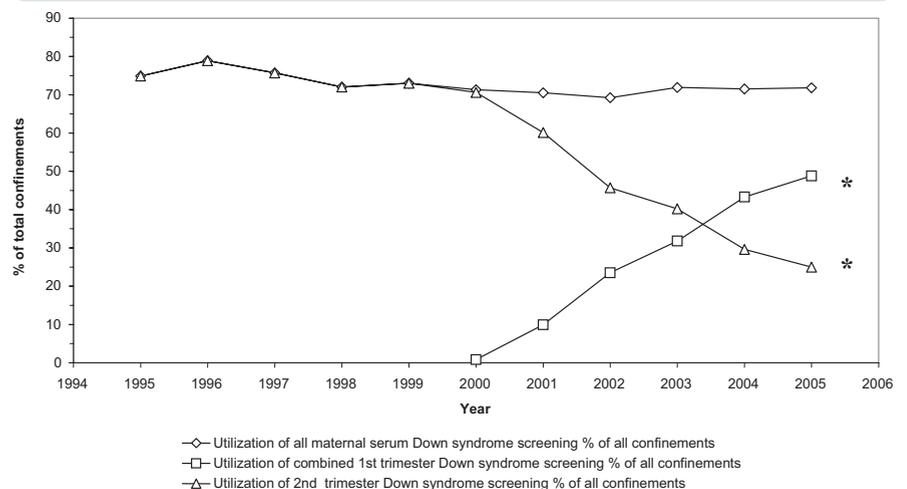
The cytogenetics laboratory in the Department of Genetic Medicine, Women's and Children's Hospital has been the sole cytogenetics laboratory to perform antenatal karyotype analysis in South Australia since 1998. A small proportion of antenatal cytogenetic analysis

was performed at a private cytogenetics laboratory from 1995 to 1998, and its data have been included. All prenatal karyotype test results from the Women's and Children's Hospital cytogenetics laboratory and the private laboratory from 1995 through 2005 were reviewed. We included as aneuploidy all cytogenetically unbalanced chromosome abnormalities (including sex chromosomal trisomies, mosaic autosomal and sex chromosomes abnormalities, and de novo cytogenetically balanced chromosome rearrangements). We excluded mosaic abnormalities that were detected by CVS that were not confirmed by amniocentesis and chromosome abnormalities that were detected in spontaneous miscarriages. Spontaneous miscarriages before 20 weeks of gestation are not karyotyped routinely in South Australia.

Confinements were defined as all women who gave birth to a baby of at least 20 weeks gestation or a birthweight of >400 g. Cases of Down syndrome included live births and stillbirths of at least 20 weeks gestation or 400 g and terminations of pregnancy at any gestation. *Cases of prenatal detection of Down syndrome* were defined as detection of Down syndrome by all antenatal screening and diagnostic modalities, which included those cases that were deemed to be at increased risk for Down syndrome by maternal serum screening or ultrasound imaging for parents who declined an invasive prenatal diagnostic test. *Prenatally diagnosed Down syndrome cases* were defined as cases of Down syndrome that were diagnosed by invasive prenatal test (CVS or amniocentesis).

We reviewed yearly data from 1995 through 2005 for total confinements, confinements for maternal age of ≥ 35 years, the use of second- and first-trimester Down syndrome screening, the uptake of invasive prenatal testing for all confinements and for those women who were ≥ 35 years old, the number of Down syndrome cases, the prenatal detection and diagnosis of Down syndrome cases, and the number of invasive prenatal tests that were needed to diagnose 1 Down syndrome and aneuploidy fetus. Chi-square tests for linear trend were performed to evaluate trends using

FIGURE 1
Use of maternal Down syndrome screening



Trends in percentage of confinements per year of the use of first-trimester maternal serum, and total Down syndrome screening from 1995 to 2005. *Chi square test for linear trend, $P < .001$.

Epi Info software (version 6; Centers for Disease Control and Prevention, Atlanta, GA). A probability value of $< .05$ was considered statistically significant.

RESULTS

There were 198,208 total confinements, for an average of 18,019 per year in South Australia from 1995 to 2005. There was no significant difference in the proportion of confinements for women who had first- or second-trimester maternal serum screening. During this period, 69%-79% of women underwent either form of maternal serum screening. There was, however, a significant decrease in second-trimester Down syndrome maternal serum screening from 75% of confinements in 1995 to 25% in 2005 ($P < .001$), and a significant increase in combined first-trimester screening from 0.8% in 2000 to 49% in 2005 ($P < .001$). This change in the use of second-trimester Down syndrome maternal serum screening coincided sharply with the introduction to South Australia of combined first-trimester Down syndrome screening in 2000 (Figure 1).

From 1995 to 2005, there were a total of 433 Down syndrome cases in South Australia, with an average of 39 cases per year. There was no significant trend in the overall prenatal detection of Down syndrome ($P = .21$) or the prenatal diag-

nosis of Down syndrome ($P = .17$), despite a significant decrease in the percent of confinements of women who underwent invasive prenatal tests from 9.3% in 1995 to 7.6% in 2005 ($P < .001$; Table). During this time period, there was no difference found in the proportion of CVS that was performed to the total number of invasive prenatal tests. CVS accounted for 13% of all invasive prenatal tests in 1995 and for 15% in 2005. We found a significant decrease in the number of invasive prenatal tests that were required to diagnose 1 Down syndrome fetus from 1 in 86 in 1995 to 1 in 40 in 2005 ($P < .001$). We also found a significant decrease in the number of invasive prenatal tests that were required to diagnose 1 aneuploid fetus from 1 in 35 in 1995 to 1 in 15 in 2005 ($P < .001$).

As expected, there was a significant increase in the proportion of confinements with maternal age of ≥ 35 years from 12.5% in 1995 to 18.7% in 2005 ($P < .001$). Despite this increase, this age group underwent less invasive prenatal testing from 43% in 1995 to 24.8% in 2005 ($P < .001$). Figure 2 shows the increase in confinements of women who were ≥ 35 years old and the decrease in invasive prenatal test in all confinements and in those women who were ≥ 35 years old.

TABLE

Number of Down syndrome cases, prenatal detection and diagnosis of Down syndrome cases, number of invasive prenatal tests, and number of invasive tests needed to detect Down syndrome and aneuploidy fetuses

Year	Down syndrome cases (n)*	Prenatally detected Down syndrome cases (n) [†]	Invasive prenatal tests (n) [‡]	Prenatally diagnosed Down syndrome cases (n) [§]	Invasive tests needed to diagnose 1 Down syndrome fetus (n)	Cases of aneuploidy diagnosed by invasive tests (n)	Invasive tests needed to diagnose 1 aneuploid fetus (n)
1995	32	23 (71.9%)	1803 (9.3%)	21 (65.6%)	86	51	35
1996	32	26 (81.3%)	2168 (11.5%)	23 (71.9%)	94	46	47
1997	41	29 (70.7%)	1914 (10.4%)	23 (56.1%)	83	50	38
1998	46	34 (73.9%)	2004 (10.9%)	33 (71.7%)	61	65	31
1999	42	30 (71.4%)	2001 (10.8%)	28 (66.7%)	71	60	33
2000	37	26 (70.3%)	1816 (10.3%)	23 (62.2%)	79	56	32
2001	36	21 (58.3%)	1623 (9.3%)	18 (50.0%)	90	55	30
2002	44	29 (65.9%)	1769 (10.0%)	27 (61.4%)	66	55	32
2003	42	34 (81.0%)	1511 (8.6%)	33 (78.6%)	46	64	24
2004	34	30 (88.2%)	1361 (7.9%)	28 (82.4%)	49	65	21
2005	47	39 (83.0%)	1364 (7.6%)	34 (72.3%)	40	91	15

* Down syndrome cases include all cytogenetically confirmed cases of live births or stillbirths of at least 20 weeks gestation or 400 g birthweight and terminations of pregnancy at any gestation.

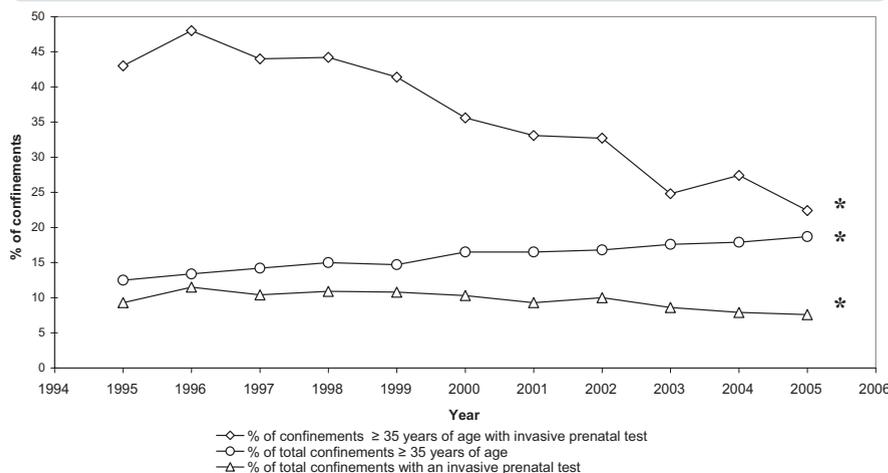
[†] Cases that were diagnosed by amniocentesis or CVS and cases that were identified as "at increased risk" by first- or second-trimester screening or ultrasound examination in which a diagnostic test was not used prenatally to confirm (chi-square test for linear trend: $P = .21$).

[‡] Prenatal invasive test: amniocentesis or CVS (chi-square test for linear trend: $P < .001$).

[§] Cases that were diagnosed prenatally by amniocentesis or CVS (chi-square test for linear trend: $P = .17$).

^{||} Chi-square test for linear trend: $P < .001$.

FIGURE 2
Trends in invasive prenatal tests in South Australia



Trends in percentage of total confinements of women who were ≥ 35 years old and the percent of confinements of women who were ≥ 35 years old and total confinements with an invasive prenatal test in South Australia from 1995 to 2005. *Chi square test for linear trend, $P < .001$.

COMMENT

We were able to demonstrate in this retrospective state/population-based audit a reduction and improved efficiency in the use of invasive prenatal tests, specifically to women who were ≥ 35 years old, after the introduction and increased use of first-trimester combined Down syndrome screening. The quality of this audit relies on South Australia's relatively stable population, an established state-wide program for obtaining outcome data, primary state maternal serum screening program, a single cytogenetics laboratory, and a record of proven ascertainment.

Translating the results of Down syndrome screening technologies from clinical trials (in which protocols are consistent and quality control measures can be monitored closely) to results in the community demand close scrutiny. Important clinical outcomes include population uptake of the offered screening tests, the effect on invasive prenatal tests, and

the actual population Down syndrome detection rates that are based on all screening modalities. These clinical outcomes will depend on numerous complex factors such as the differences in demography, patient access to screening technologies, quality control parameters, patient preferences, and clinician biases. Indeed, one would not expect community- or state-based screening programs to reach the level of detection that is seen in clinical trials. Several population-based studies have reported the impact of the introduction of second-trimester Down syndrome screening on clinical outcomes,^{13,14} which includes 1 from South Australia.¹⁵ First-trimester combined screening, however, includes serum markers and nuchal translucency, for which technical expertise is required¹⁶ and had led to a cautious approach in advocating the introduction of first-trimester combined Down syndrome screening to the community.¹⁷ Indeed, 2 large population studies, 1 from Scotland¹⁸ and the other from Western Australia,¹⁹ demonstrated very different results with first-trimester combined Down syndrome screening, thus emphasizing the impact of differences of clinical practice and sonographic technique. The Down syndrome screening program from Western Australia was demographically and technically similar to that in South Australia, but O'Leary et al¹⁹ did not comment on the effect that first-trimester Down syndrome screening had on other clinical parameters (such as the use of screening modalities and invasive prenatal tests), which was the aim of our study.

We were not surprised by the accelerated use of first-trimester combined Down syndrome screening after its introduction in South Australia in 2000. Women's preference for earlier Down syndrome screening has been documented^{20,21} and appears to be related to earlier reassurance and the emotional and technical advantages of the option of earlier pregnancy terminations.²² One might expect, with the increased use of first-trimester combined screening and the desire for earlier aneuploidy diagnosis, that there would be an increased proportion of women with invasive testing

who undergo CVS. This was not found in our study. The CVS proportion of invasive prenatal tests has remained low in South Australia and may reflect consumer choice that is based on the counselling that is provided by medical practitioners and some limitation of access to first-trimester invasive prenatal testing. Fortunately, under Australia's universal health care coverage, which is paid for by a compulsory income tax levy (Medicare), there is no patient disincentive to choose either first- or second-trimester Down syndrome screening or 1 particular type of invasive prenatal testing. Screening programs should take into account that there are differences in patient preferences, access to CVS, and efficient protocols for patient notification of screen-positive results. If patient autonomy for the early detection of Down syndrome is to be accepted truly, then scrutiny of clinician counselling practices, training in early invasive prenatal tests, and prompt notification of screen-positive results are required. The percentage of confinements that use either first- or second-trimester screening remained the same through this time period, which suggests that the introduction of first-trimester screening had no effect on those women who generally decline any form of Down syndrome screening. A concern of the reduced use of second-trimester maternal serum screening is the impact on the detection of neural tube defects. The benefit of the addition of MSAFP to ultrasound evaluation in the detection of neural tube defects has been demonstrated previously,²³ and offering MSAFP to all women is advocated commonly.²⁴ The possible negative effect on the community neural tube defect detection rate by "trading" second-trimester maternal screening for first-trimester combined screening should be evaluated.¹⁷ Second-trimester MSAFP screening for neural tube defects, although available, is not offered routinely to South Australian women who have had first-trimester combined Down syndrome screening. We currently are reviewing trends in antenatal neural tube defect detection rates in South Australia in light of improvements in ultrasound technology and ex-

pertise with the decrease in the use of second-trimester MSAFP.

We were able to demonstrate over this period a trend towards an improved efficiency in the state-based Down syndrome screening. The steady decrease in invasive prenatal testing appears to accelerate with the marked increase in use of first-trimester combined screening. This contrasts to the introduction of second-trimester maternal serum screening to South Australia in 1991, after which the rate of invasive prenatal testing doubled from 4.9% in 1986 to 11.4% in 1996.¹⁵ Further effectiveness in the screening program was demonstrated with the number of invasive prenatal tests that were needed to detect 1 Down syndrome or aneuploidy fetus, which showed a significant decrease from 1995 to 2005. This significant decrease coincides with the introduction of first-trimester combined Down syndrome screening in 2000. Benn et al²⁵ showed a similar trend in the 1990s and attributed this to the use of maternal serum screening and ultrasound evaluation, rather than to maternal age, to assess risk. We would assume the changes that are found in our study are related to a similar desire in South Australia to use new technologies to assess or readjust the individual Down syndrome risk.

The decrease in total invasive prenatal tests in our review appears to be related to the marked decrease in invasive prenatal tests in women who are ≥ 35 years old. This most likely represents both clinician and patient confidence in first-trimester combined screening to adjust age-related Down syndrome risk and follows similar patterns that have been seen with second-trimester maternal serum screening⁶ and recently with first-trimester nuchal translucency screening.²⁶ This audit confirms our ability to better define the "high-risk women", which reduces the use and risk of invasive prenatal testing. Indeed, there had been a concerning trend of an increasing maternal serum screen-positive rate in South Australia. This is related most likely to the increase in maternal age and the use of serum screening in this older age group during that time period. With the increased use of first-trimester com-

bined screening and recalculation of the risk cut-off values from 1 in 405 to 1 in 300 in South Australia, we have been able to reduce that trend without affecting overall Down syndrome prenatal detection rates.

There are several limitations of our review. As a retrospective audit, there is the risk of outcomes not being reported adequately to the South Australian Birth Defects Register, patient migration to and from South Australia, and fetal loss bias in which loss occurs after screening and before birth. We cannot assess directly whether the trend in decreasing invasive prenatal tests was the result of first-trimester combined Down syndrome screening or the change of the risk cut-off value from 1 in 405 to 1 in 300. However, despite a higher screen-positive threshold, there was a general trend (although not statistically significant) in overall improved prenatal Down syndrome detection rates with the use of all detection modalities, particularly when the use of first-trimester combined Down syndrome screening reached >30% of total confinements (detection of >80%). This would suggest that the introduction of first-trimester combined Down syndrome screening to South Australia had a significant impact on the efficiency and effectiveness of the state-based Down syndrome screening program. Another limitation is the difficulty of the direct assessment of the effect of the introduction of other new technologies on our results. Ultrasound evaluation has been shown to have an impact on Down syndrome risk assessment on the basis of age²⁷ and first-trimester combined screening.²⁸ The impact of the advances in ultrasound evaluation on the use of invasive prenatal testing was not assessed in our study, because indications for invasive prenatal testing are not reported commonly to the cytogenetics laboratory. We cannot therefore assert a cause and effect as an explanation for the trends that were observed. Nevertheless, through a direct state/population-based program with continuous communication between screening laboratories, certified ultrasound

units, South Australian outcome registers, and a single cytogenetics laboratory, we were able to portray accurately informative trends of the use of a new technology and its association with trends of the use of invasive prenatal testing.

In conclusion, we were able to demonstrate positive trends in the effectiveness, the efficiency, and the ability to define pregnancies that were at increased risk for Down syndrome in South Australia after the introduction of a state-based first-trimester combined Down syndrome screening program. As new Down syndrome screening technologies are introduced after robust clinical trials, a centralized state-based program will allow the assessment of the impact that these new technologies will have on the community. ■

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