GENETICS

Cost-effectiveness and accuracy of prenatal Down syndrome screening strategies: should the combined test continue to be widely used?

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OBJECTIVE: We analyzed the cost-effectiveness (CE) and performances of commonly used prenatal Down syndrome (DS) screening strategies.

STUDY DESIGN: We performed computer simulations to compare 8 screening options by applying empirical data from Serum, Urine, and Ultrasound Screening Study trials on the population of 110,948 pregnancies. Screening strategies outcomes, CE ratios, and incremental CE ratios were measured.

RESULTS: The most CE DS screening strategy was the contingent screening method (CE ratio of Can$26,833 per DS case). Its incremental CE ratio compared to the second-most CE strategy (serum integrated screening) was Can$3815 per DS birth detected. Among the procedures respecting guidelines, our results identified the combined test as the screening strategy with the highest CE ratio (Can$47,358) and the highest number of procedure-related euploid miscarriages (n = 71).

CONCLUSION: In regard to CE, contingent screening is the best choice. The combined test, which is the most popular screening strategy, shows many limitations.

Key words: cost-effectiveness, Down syndrome, prenatal screening

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In the last 15 years, major advancements have been made in Down syndrome (DS) prenatal screening.[1,2] However, there is still no consensus on the optimal strategy that should be offered to pregnant women. Actually, neither Canada nor the United States has adopted a national strategy[3,4] and screening practices largely differ across North America.[5,6] Matched to worldwide-advised procedures,[7,8] 6 screening options respecting guidelines in Canada and the United States are available:[5,6] quadruple, combined, integrated, and serum integrated tests, and stepwise sequential (sequential) and contingent sequential (contingent) screenings.

Whereas pretest counseling should be available to patients so that they can make an informed choice for screening procedures,[5] the literature is insufficient to help clinicians choose among the options proposed. The risks and benefits of each strategy have been partially reported on different populations[4,9,10] and a detailed analysis of the cost-effectiveness (CE) of these options on the same model is lacking. So far, most analyses published have not used empirical data,[11-13] have applied inappropriate statistical approaches,[11,14] or have compared the CE of invasive tests vs no diagnosis.[15,16] Evaluation of 3 strategies combining first- and second-trimester analyses[4,10] (contingent, sequential, and integrated screenings) has been reported with limited and contradictory results: Ball et al[4] demonstrated that contingent screening dominated the integrated test, whereas Wald et al[10] concluded that integrated screening had the best screening performance. Many authors have addressed concerns regarding the lack of data about these 3 screening strategies.[3,10,17,18] Given the numerous screening options available,[18,19] it is unlikely that any single empirical or clinical study could compare all the strategies available with acceptable external validity. Computer simulations are an elegant alternative to identify which strategy is likely to be the most CE.[4,10,11,20] We recently reported the impact of various risk cutoffs in first trimester on their CE.[21] The objective of the current study is to compare all commonly used screening strategies including the quadruple and the serum integrated tests, but also the combined test, since first-trimester screening has become the de facto stan-

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dard of care in the United Kingdom, France, and the United States, while the rest of North America may follow suit.[4,22,23]

MATERIALS AND METHODS

Design

Using the modeling approach previously developed,[21] a decision analysis was performed through the computation of expected outcomes resulting from the DS screening options tested. Data simulations were performed on a virtual population of 110,948 pregnancies with demographic (maternal age distribution), genetic, and phenotypic (regarding DS) characteristics of the Quebec, Canada, population.[21] By this approach we simulated the costs and outcomes of all options considered. The Figure presents a simplified version of the decision model.

Screening options and endpoints

Analyses were run to analyze the CE (global costs, CE ratios [costs per DS diagnosed], and the incremental CE ratios [ICER])[20] of 8 screening options (quadruple, combined, integrated, and serum integrated tests; sequential and contingent screenings; maternal age alone [≥35 years]; and the triple test) from a public health perspective and to compare their performance estimates for an overall 90% detection rate by evaluating 7 other relevant endpoints that cover the main outcomes in DS prenatal screening:[10,20] the false-positive rate, which defines the number of scheduled amniocentesis procedures; the number of procedure-related euploid miscarriages; the number of DS live births; the number of unnecessary terminations; the proportion of DS pregnancies screened by a first-trimester test; the proportion of patients reassured in early gestation through first-trimester testing; and the proportion of continuing pregnancies that proceed to second-trimester testing. The ICER represents the ratio of the difference in the cost of 2 screening strategies divided by the difference in outcome (additional DS case diagnosed) of the 2 techniques.

Sequential and contingent screenings

Given the published data for sequential and contingent screenings,[10] the first-trimester high-risk cutoff we applied was 1 in 30, and in the contingent screening approach, the lower risk cutoff used on the first test was 1 in 2000.

Diagnosis tests

Simulated diagnostic procedures are contingent on the timing of the screening test results. To evaluate the impacts of screening tests based on the gold standard of prenatal care, only amniocentesis was used in prenatal diagnosis following second-trimester screenings results. However, for women who tested positive in the first-trimester screening, transabdominal chorionic villous sampling (CVS) karyotyping was considered. Timing and rate of procedure-related euploid miscarriages depends on the tests undergone. The model also takes into account diagnostic test performance characteristics (amniocentesis and CVS).[24]

Data

The screening markers and procedures used are shown in Table 1. All input variables and their sources are presented in Table 2.

Probabilities

DS-affected pregnancy, DS-unaffected pregnancy, and miscarriage risk probabilities

Using the modeling approach previously developed,[21] trimester-specific DS risks were used to modify the number of DS cases that would be identified in each trimester due to spontaneous fetal losses. The rates of DS pregnancy losses seemed to be more important in our model (52%)[21] than in other series (43%[25-27] and 30%[28,29]) because part of these DS pregnancies are comprised of the voluntary pregnancy terminations in first and second trimester observed in our population in 2001. These DS pregnancies and their evolution are also simulated in our model because some of these DS pregnancies could access prenatal diagnosis at the first but not at the second trimester.

Test performance

The distribution of Serum, Urine, and Ultrasound Screening Study (SURUSS) marker results in DS-affected and DS-unaffected pregnancies was used to determine the parametric values.[9,10] All false-positive rates and risk cutoffs were standardized to the same gestational age (11 weeks' gestation) for first-trimester measurements.

Other probabilities

The estimated compliance for the Quebec, Canada, population[21] (ie, the proportion of women who consent to participate in DS prenatal screening) to undergo a diagnostic test after a positive screening test result and to choose elective abortion after a positive diagnostic test was included in the calculations. Depending of the screening procedure used, when a second-trimester testing is indicated, all women were considered to comply with the scheduled testing.

Costs

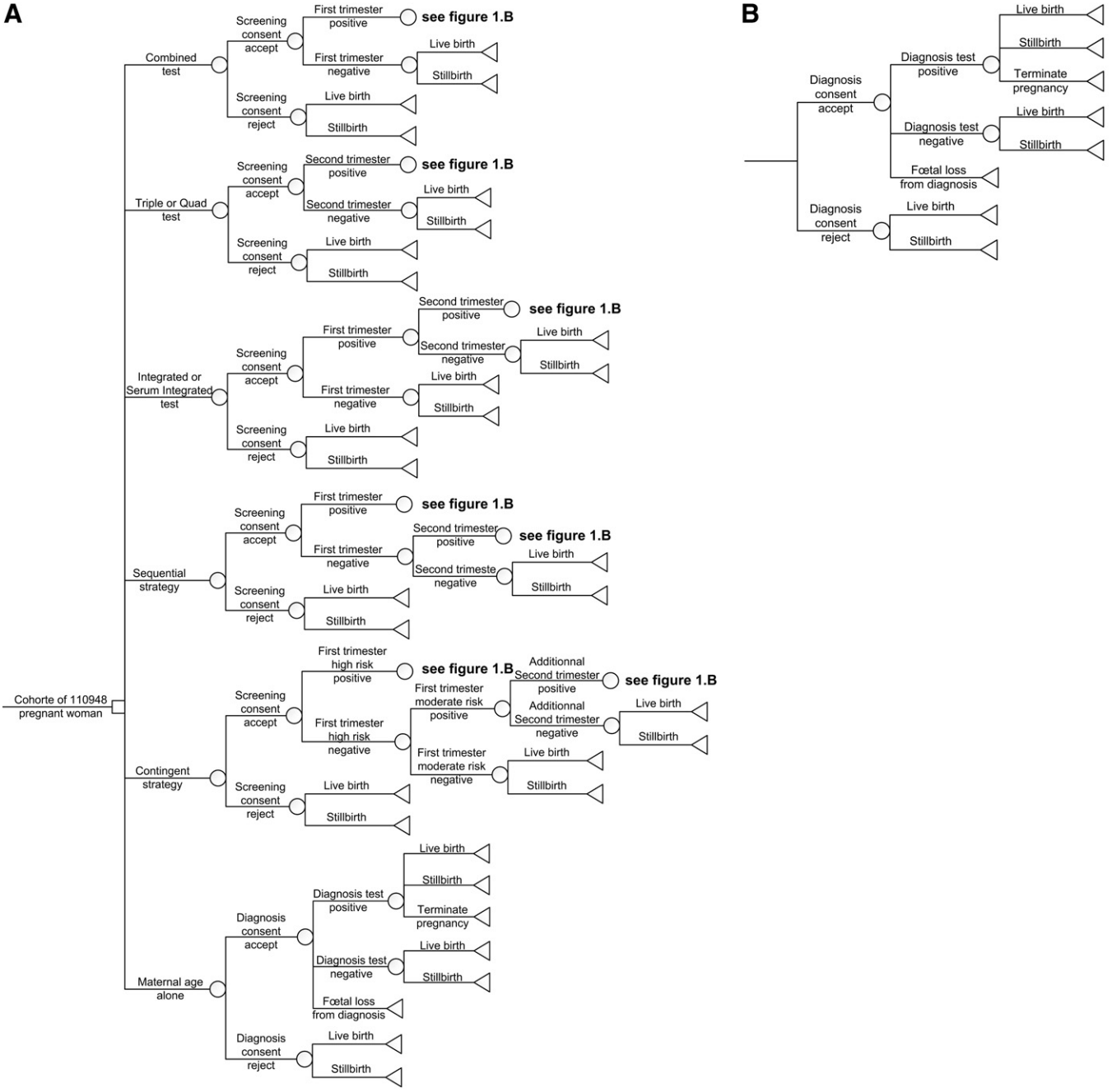
In Canada, in accordance with the Canadian Health Care Act, all medically necessary services are provided under the public health care system and are free of charge. Only the direct costs-from a Ministry of Health and Public Medical Insurance perspective-were considered. Government databases (financial and operational databank [Système d'Information Financière et Opérationnelle] and All Patient Refined Diagnosis Related Groups) were used from 2005 through 2007 to calculate average unit prices.[21] Provincial technical units were used for laboratory and imaging tests.[21] Unit prices were marked up to include supportive activity centers by using the direct approach.[30]

Costs reported in Table 2 for screening tests do not reflect the cost of 1 procedure but the mean for all medically necessary services provided for each screening option. Items considered for costing included screening costs as well as health care and medical services related to the following outcomes: birth, spontaneous miscarriage, elective abortion, or procedure-related euploid miscarriages. Costs are expressed in Canadian dollars. Exchange rate in 2007 was Can$1.07 = US$1.00.

CE analysis

Our approach follows methodological guidelines for CE analysis in prenatal di-

FIGURE
Simplified versions of decision trees



A, Screening option algorithms. **B**, Diagnosis procedure algorithms. Not shown in this simplified depiction, but included in our model, is possibility for miscarriage to occur before testing or after results.

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agnosis.[20] All measured costs occurred within 1 year; therefore, there was no need to discount costs and effects over time.[20] Univariate sensitivity analyses[21] were performed on the rate of consent to participate in prenatal screening (65% and 80%), the rates of fetal loss from CVS (0.5%, 1%, and 2%), the rates of fetal loss from amniocentesis (1% and 1.5%), and the proportion of couples with a confirmed DS fetus that would undergo pregnancy termination (70% and 80%). Moreover, the DS screening strategies sensitivities and false-positive rates were varied over the ranges achieved in the SURUSS trial.[9,10]

Estimation of confidence intervals

To generate 95% confidence intervals on CE ratio estimates, a bootstrap method was used[31] as previously employed.[21]

TABLE 1
Definitions of screening procedures

Combined test	First-trimester test based on combining NT measurement (NT, ultrasound measurement of width of area of translucency at back of fetal neck early in pregnancy) with free β-hCG, PAPP-A, and maternal age.
Triple test	Second-trimester test based on measurement of AFP, uE3, and hCG (either total hCG or free β-hCG) together with maternal age.
Quadruple test	Second-trimester test based on measurement of AFP, uE3, free β-hCG (or total hCG), and inhibin-A together with maternal age.
Integrated test	Integration of measurements performed at different times of pregnancy into single test result. Unless otherwise qualified, "integrated test" refers to integration of NT and PAPP-A in first trimester with quadruple test markers in second. First-trimester screening marker results are not analyzed until second-trimester markers are evaluated, at which point they are both assessed together.
Serum integrated test[1]	Variant of integrated test without NT (using PAPP-A in first trimester and quadruple test markers in second trimester).
Sequential screening[47]	Screening in which first-trimester test is performed (NT, free β-hCG, and PAPP-A) and result is interpreted immediately. If this is positive, diagnostic test is offered (CVS), but if it is not positive, second-trimester serum markers are measured (quadruple test markers) and first-trimester markers are reused to form integrated test.
Contingent screening[48]	Screening in which first-trimester test (NT, free β-hCG, and PAPP-A) is used to triage population of women screened into 3 groups: 1 group (high-risk screen-positive) that is immediately offered diagnostic test (CVS), second group (screen-negative) that receives no further screening, and third intermediate group (or lower-risk screen-positive) that has second-trimester markers measured (quadruple test markers) and first-trimester measurements reused to form integrated test.

AFP, alpha-fetoprotein; *CVS*, chorionic villous sampling; *hCG*, human chorionic gonadotrophin; *NT*, nuchal translucency; *PAPP-A*, pregnancy-associated plasma protein A; *uE3*, unconjugated estriol.

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RESULTS

CE analysis

The CE analysis results are summarized in Table 3. The most CE DS screening strategy was the contingent screening method (CE ratio of Can$26,833 per DS). The ICER of the contingent screening method compared to the second-most CE strategy (serum integrated screening) was Can$3815 per DS birth detected. The combined test was more efficient than the contingent test but its ICER using SURUSS data (combined test$^{8.4\%}$) compared to the contingent screening was Can$369,391 per additional DS screened.

The screening strategy based on maternal age alone was the least CE option. These results appeared robust in sensitivity analyses where we varied the rate of consent to participate in prenatal screening, the rate of fetal loss from CVS, the rate of fetal loss from amniocentesis, the proportion of couples with a confirmed DS fetus that would undergo pregnancy termination, and the DS strategies sensitivity and false-positive rates. None of these different models yielded a different relative rank of the various screening scenarios analyzed (data not shown).

Screening strategy outcomes

Table 4 reports the results on endpoints considered for each screening strategy. With respect to contingent and sequential screening strategies, we report very similar results on major outcomes (false-positive rate, procedure-related euploid miscarriages, unnecessary terminations, and DS pregnancies screened by a first-trimester test). However, the contingent screening, in the group of strategies associated with a low rate of procedure-related miscarriages (≤10), is the only option that allowed 78.4% of patients to be reassured in the first trimester and 79.0% of women to avoid retesting in the second trimester. The combined test was associated with the highest rate of DS pregnancies screened positive in first trimester (89.9%); however, it was also associated with the highest number of procedure-related euploid miscarriages (n = 71) and the highest number of unnecessary terminations (n = 24).

COMMENT

We found that the contingent screening is actually the most CE strategy for prenatal DS screening. According to our model, we also found that integrated test strategy has the lowest rate of procedure-related miscarriages. These findings are different from prior reports that suggested that the combined test could be more CE than second-trimester testing.[12,13,32] Our results identified the combined test as the screening strategy respecting guidelines with the highest cost, probably for 3 reasons: its requirement of a nuchal transparency measurement and the high false-positive rate and number of unnecessary terminations associated with it. The combined test was also associated with the highest number of procedure-related euploid miscarriages.

The false-positive rate we used in our study for the combined test was 8.4% for a detection rate of 90% as revised by the SURUSS research group.[33] This is in accordance with the false-positive rate reported by Malone et al[34] in the First and Second Trimester Evaluation of Risk (FASTER) trial for first-trimester screening since at 11 weeks the observed false-positive rate was 3.8% for a detection rate of 85% and 18% for a detection rate of 95%. Since other prospective trials evaluating first-trimester screening have reported a better efficiency

TABLE 2
Analysis input variables

Screenings, diagnosis tests, or events	Cost (Can$)	References
Combined test[8.4%]	40.00	32,49-51
Triple test	15.00	21
Quadruple test	25.00	49-51
Integrated test	65.00	21
Serum integrated test	35.00	49-51
Sequential screening	105.00	21
Contingent screening	55.00	21
Consulting with genetic counselor	73.90	21
CVS diagnostic procedure	876.00	21
Amniocentesis diagnostic procedure	500.00	21
Termination of pregnancy	1357.33	21
Variables of screening tests with 90% detection rate	**False-positive rate (%)**	
Combined test (1/625 cutoff)	8.4	32,52
Triple test (1/650 cutoff)	14.70	9,52
Quadruple test (1/545 cutoff)	10.60	9,52
Integrated test (1/230 cutoff)	2.11	9,52,53
Serum integrated test (1/355 cutoff)	5.30	9,52
Sequential screening (1/30 cutoff, first trimester)[a]	2.25	10,21
Contingent screening (1/30 cutoff, first trimester)[a]	2.42	10,21
Events before or after screening and diagnostic intervention	**Probability (%)**	
Consent to participate in prenatal screening	70.0	21
Consent for amniocentesis or CVS with screening positive	90.0	21
Fetal loss from amniocentesis	0.5	21,23,54-57
Fetal loss from CVS	1.6	21,23,54-57
Proportion who terminated pregnancy with fetal DS	90.0	21

CVS, chorionic villous sampling; *DS*, Down syndrome.

[a] Lower risk cutoff used on first test was 1 in 2000.[10]

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of this screening strategy (5% false-positive rate for a 90% detection rate[35]), we also simulated the CE by using the data: we obtained, respectively, Can$36,632 (Can$36,199-37,066) and Can$174,019 for CE ratio and ICER compared to contingent screening scenario, confirming the costs of the combined test (Table 3). Moreover, according to our findings, the combined test (false-positive rate of 8.4%) induces 12 times more procedure-related euploid miscarriages than the integrated test whereas it was recently proposed that this is the main outcome to reduce in DS prenatal screening.[36] Interestingly, it is worth mentioning that first-trimester screening has become the de facto standard of care in the United Kingdom, France, and the United States, while the rest of North America may follow suit.[4,22,23] Indeed, the combined test has been recently shown to be extensively used since it is the most popular screening strategy in the United States for 2007: this screening is used by 56% of maternal-fetal medicine specialists whereas the contingent screening is used only by 11.8% of them.[37]

Our study shows that the integrated test also results in a very low number of procedure-related euploid miscarriages and unnecessary terminations because it allows for a diagnostic test only in the second trimester. Indeed, too early a diagnosis may produce an excess in unnecessary terminations of the DS cases screened[10] since a spontaneous miscarriage may occur between the first and second trimesters.[28] But, if an integrated test was universally applied, no DS pregnancy would be detected and no patients could be reassured in the first trimester. This could be a disadvantage given that even if some studies suggest that women prefer a lower number of procedure-related euploid miscarriages,[38,39] others suggest that women also want an early diagnosis.[40,41] Also, routine nondisclosure of first-trimester risk assessments may not be acceptable to patients in clinical practice, and withholding results may violate sound ethical principles of medical practice.[18]

Our results highlight the advantages of implementing a serum integrated test compared to a quadruple test[6] and the quadruple test compared to a triple test.[4] Additional use of serum markers results in the reduction of screening's false-positive rate.

There are 2 important limitations of our study: the lack of prospective data and the geographic and health care heterogeneity across countries that could affect the external validity of our results.

Notably, availability of pregnancy termination and the politics surrounding abortion in general may direct patient choices as much as health policy. Although our study is based on computer modeling, rather than prospective data, our results are strengthened by the use of empirical data and true health care costs. Given geographic differences and countless screening strategies, it is unlikely that a large-scale prospective clinical trial comparing these 8 screening approaches could rapidly be organized across North America. The procedure used in this work is particularly powerful because a large number of strategies could be simultaneously simulated to compare several individual DS screening programs.[11,42,43] All the reported CE ratios

TABLE 3
Cost-effectiveness analysis of Down syndrome screening strategies

Strategies[a]	Global costs, million Can$ (95% CI)	Effectiveness[b] (95% CI)	CE ratios, Can$ (95% CI)
Contingent screening	2.8579 (2.814–2.902)	106.51 (95.1–117.9)	26,833 (24,008–29,815)
Serum integrated test	2.7906 (2.786–2.795)	88.87 (87.7–90.0)	31,401 (31,119–31,962)
Sequential screening	3.7440 (3.701–3.787)	106.32 (94.8–117.9)	35,215 (31,494–39,148)
Integrated test	3.2610 (3.228–3.431)	90.35 (79.5–97.8)	36,089 (33,325–40,861)
Combined test$^{5\%}$	4.1613 (4.153–4.170)	114.00 (112.7–115.3)	36,632 (36,199–37,066)
Quadruple test	3.4413 (3.435–3.448)	88.19 (87.1–89.0)	39,021 (38,686–39,667)
Triple test	3.8324 (3.760–3.904)	87.48 (74.8–100.2)	43,809 (37,247–50,871)
Combined test$^{8.4\%}$	5.3476 (5.336–5.359)	113.25 (112.0–114.5)	47,358 (46,851–47,855)
Amnio ≥35 y	4.1549 (4.124–4.185)	56.12 (51.5–60.7)	74,037 (68,001–80,331)

Screening strategies are presented according to their CE ratios (per 100,000 pregnancies under prenatal care and for overall 90% detection rate; CI: 95%).
CE, cost-effectiveness; *CI*, confidence interval.

[a] Combined test$^{5\%}$ simulated with Nicolaides et al[35] data (5% false-positive rate for 90% detection rate) and combined test$^{8.4\%}$ simulated with Serum, Urine, and Ultrasound Screening Study data[9] (8.4% false-positive rate for 90% detection rate); [b] Effectiveness: number of Down syndrome cases detected through screening test.

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were computed in the context of Quebec province health care system and costs. However, with respect to cost comparison, relative costs (ranking of different scenarios) usually are more comparable (ie, approaches that are most CE in one setting are likely to also show good performance in different conditions). Also, given the robustness of our findings observed in the sensitivity analyses where we varied the values of the major assumptions of the modeling, it is likely that the relative performance (or ranking) of various scenarios would be similar in other jurisdictions. The fetal loss we used in our modeling was 1 in 200 from amniocentesis and 1.6% from CVS and is based on published data.[24] Nevertheless, a recent review[44] on procedure-related risks for prenatal diagnosis techniques reports the difficulty to establish precise rates because of various possible biases for estimated fetal losses in published data. This review used data from randomized controlled trials as well as from systematic reviews and national registries, and concluded that the more suitable procedure-related miscarriage rate was 0.5-1.0% for amniocentesis.[44] Also, the procedure-related miscarriage risk of CVS is not well established since 3 other recent reviews report miscarriage rates, respectively, of 1.3%,[45] 1.4%,[46] and 1.9%.[47] As recently suggested,[44] single-center studies with remarkably good results due to very skilled operators[48,49] cannot be used for general counseling, and the very low procedure-related risk of 1 in 1600 attributable to amniocente-

TABLE 4
Performances of Down syndrome screening strategies on relevant endpoints that cover main outcomes in Down syndrome prenatal screening

Strategies	False-positive rate, %	Procedure-related euploid miscarriage	DS live births	Unnecessary terminations	DS pregnancies positive in first-trimester test, %	Patients reassured early in gestation by first-trimester testing, %	Pregnancies that proceed to second-trimester testing, %
Contingent screening	1.65	10	64	18	66.1	78.4	21.0
Serum integrated test	3.70	12	63	3	0.0	0.0	100.0
Sequential screening	1.54	10	63	18	66.0	0.0	99.3
Integrated test	1.82	6	64	3	0.0	0.0	100.0
Quadruple test	7.43	23	63	3	0.0	0.0	100.0
Triple test	10.28	31	64	3	0.0	0.0	100.0
Combined test$^{8.4\%}$	5.88	71	75	24	89.9	91.4	0.0
Amniocentesis ≥35 y	0.00	41	74	7	0.0	0.0	0.0

Screening strategies are presented according to their cost-effectiveness ratios. Overall 90% detection rate per 100,000 pregnancies under prenatal care.
DS, Down syndrome.

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sis suggested by the FASTER trial[50] may be due to the use of nonrandomized control group with significant bias.[45] The demographic characteristics of the population simulated are comparable with other Western countries. Especially, the mean maternal age and the proportion of women aged ≥35 years were comparable to the SURUSS[9] and the FASTER trial's[34] populations, which represented women in the United Kingdom and the United States. The effect of the maternal age distribution has been reported to be limited and unlikely to be large enough to influence DS screening policy decisions.[51] We evaluated the 6 screening options of the US and Canadian guidelines on the same model population that is attractive. Indeed, data reported that cover the performances of these strategies were generally obtained from different populations and study models that introduce possible biases for a global comparison. In our article, the relative performances of these scenarios were evaluated using the same population, the same health care costs, and identical parameters except those pertaining to the DS screening scenarios themselves.

Finally, one could suggest that there is an apparent bias in comparing the cost for each DS pregnancy detected by screening completed in the first vs second trimester since it would favor early detection though identifying affected pregnancies that spontaneously miscarry before the 16th week of pregnancy. Nevertheless, in the reported data, we estimated the cost per DS detected at the possible time of detection (first vs second trimester) depending on the screening procedure used and we reported the global cost of each screening strategy, which is independent from the number of DS cases detected. To compare first- vs second-trimester screening procedures on a common ground, we used a fixed detection rate, which is more applicable than a fixed false-positive rate, because a fixed false-positive rate applied in first trimester compared to second trimester induces a different detection rate, notably from the spontaneous fetal losses of DS fetuses between first and second trimester.[52] We chose the 90% detection rate because, given published data for screening procedures using first- and second-trimester tests, test performances and cutoffs used were specified for all of these screening tests (integrated,[9] sequential, and contingent screening tests[10]) at this detection rate. Also, for April 2010 the United Kingdom National Screening Committee targets a detection rate of >90%.[7]

CONCLUSIONS

Our results suggest that patients seen early in their pregnancy may benefit from being offered screening that combines first- and second-trimester evaluations[53] to allow for a high DS detection rate[18,53] combined with a low rate of procedure-related miscarriages. We show that while the integrated test seems to be the strategy with the lowest rate of procedure-related miscarriage, the contingent strategy seems to be the most CE and is associated with an attractive rate of procedure-related euploid miscarriages and unnecessary terminations. Moreover, this screening option provides a majority of women with reassurance early in gestation and may minimize costs by limiting retesting. We demonstrate that the combined test has many limitations in the population context that was tested but is still a realistic representation of Western populations. Our results should not be used to condemn any current practice of prenatal diagnosis of DS, as CE analyses are only 1 element among many that need to be taken into account in the decision of what strategy is the most appropriate for a given population or for a given woman. Nevertheless, if as previously stated,[53] some couples opt for this screening strategy to obtain information at an earlier stage of pregnancy, who will assume the additional costs induced by this personal choice? ■

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