Original Research

First- and Second-Trimester Evaluation of Risk for Down Syndrome

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OBJECTIVE: To investigate the differences in costs and outcomes of Down syndrome screening using data from the First and Second Trimester Evaluation of Risk (FASTER) Trial.

METHODS: Seven possible screening options for Down syndrome were compared: 1) Triple Screen—maternal serum alpha fetoprotein, estriol, and hCG; 2) Quad—maternal serum alpha fetoprotein, estriol, hCG, and Inhibin A; 3) Combined First—nuchal translucency, pregnancy-associated plasma protein A (PAPP-A), free β-hCG; 4) Integrated—nuchal translucency, PAPP-A, plus Quad; 5) Serum Integrated—PAPP-A, plus Quad; 6) Stepwise Sequential—Combined First plus Quad with results given after each test; and 7) Contingent Sequential—Combined First and only those with risk between 1:30 and 1:1,500 have Quad screen. The detection rates for each option were used given a 5% false-positive rate except for Contingent Sequential with a 4.3% false-positive rate. Outcomes included societal costs of each screening regimen (screening tests, amniocentesis, management of complications, and cost of care of Down syndrome live births), Down syndrome fetuses identified and born, the associated quality-adjusted life years, and the incremental cost–utility ratio.

RESULTS: Based on the screening results derived from the 38,033 women evaluated in the FASTER trial, the Contingent Sequential screen dominated (lower costs with better outcomes) all other screens. For example, the Contingent Sequential cost 32.3 million dollars whereas the other screens ranged from 32.8 to 37.5 million dollars. The Sequential strategy led to the identification of the most Down syndrome fetuses of all of the screens, but at a higher cost per Down syndrome case diagnosed ($719,675 compared with $690,427) as compared with the Contingent Sequential. Because of the lower overall false-positive rate leading to fewer procedure-related miscarriages, the Contingent Sequential resulted in the highest quality-adjusted life years as well. The Contingent Sequential remained the most cost-effective option throughout sensitivity analysis of inputs, including amniocentesis rate after positive screen, rate of therapeutic abortion after Down syndrome diagnosis, and rate of procedure-related miscarriages.

CONCLUSION: Analysis of this actual data from the FASTER Trial demonstrates that the Contingent Sequential test is the most cost-effective. This information can

See related editorial on page 2.

** For a listing of other members of the FASTER Research Consortium, see the Appendix.*

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help shape future policy regarding Down syndrome screening.
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First-trimester screening for Down syndrome using nuchal translucency measurement alone or in conjunction with serum levels of certain analytes has become increasingly widespread, since first conceived by Nicolaides and other investigators.[1,2] Several European and U.S. studies[3–6] have documented that strategies that include nuchal translucency can reach sensitivities of up to 90% at low false-positive rates. Evaluation in the first trimester also allows incorporation of these first-trimester results with the current standard-of-care second-trimester serum screening.[7] The First and Second Trimester Evaluation of Risk (FASTER) Trial[6] compared first-trimester screening with nuchal translucency and serum analytes (PAPP-A and free β-hCG) directly to the Quad Screen (second-trimester maternal serum alpha-feto protein, estriol, β-hCG, and Inhibin-A) as well as combinations of these markers

Since the FASTER Trial was designed and executed, additional screening strategies for identifying Down syndrome fetuses have evolved using the same tests. These are the concept of Stepwise Sequential screening[8] and Contingent Sequential screening.[9] In the former, results are provided to patients after both the first- and second-trimester components of the test, with all patients who are initially screen negative being screened again in the second trimester. In this case the second-trimester screening analyses take into account the results of the earlier first-trimester screen for any given individual. Contingent Sequential screening also begins with combined first-trimester screening using both nuchal translucency and first-trimester serum screen. However, based on these results, there are three options: 1) high risk–these women are offered invasive prenatal diagnostic testing; 2) moderate risk–these women go on to get second-trimester serum screening; and 3) low risk–these women obtain no further testing.

Data in the literature so far primarily focus on detection rates of the different strategies for screening for Down syndrome. Cost-effectiveness analyses for Down syndrome screening that have been reported to date have been based on modeled rather than actual data.[10–12] Whereas detection rates are important for any given individual, the cost-effectiveness of these screening strategies is critical information for development of optimal public health strategies for Down syndrome detection in the general population. In the current analysis, we use actual data from the FASTER trial to examine the cost-effectiveness of first and second-trimester screening strategies for Down syndrome.

MATERIALS AND METHODS

The FASTER study was approved by the individual institutional review boards at each one of the study sites. A decision analytic model was developed with seven primary branches: 1) Triple Screen–maternal serum alpha fetoprotein (AFP), estriol, and hCG; 2) Quad Screen–maternal serum AFP, estriol, hCG, plus Inhibin A; 3) Combined First–nuchal translucency, pregnancy associated plasma Protein A (PAPP-A), and free β-hCG; 4) Integrated–nuchal translucency, PAPP-A plus Quad, with result provided after all tests completed; 5) Serum Integrated–PAPP-A plus Quad without nuchal translucency; 6) Stepwise Sequential–Combined First plus Quad with results given after each test; and 7) Contingent Sequential–Combined First triple screen, only those with risk between 1:30 and 1:1,500 have Quad Screen. Essentially, once a screening test is used, the patient can get a positive or negative result. If the result is positive, patients can choose whether to undergo definitive karyotypic diagnosis. If this arm is chosen, patients will either undergo a spontaneous abortion, receive results of aneuploidy, or normal results. Furthermore, to evaluate the tests on equal grounds, only amniocentesis for prenatal diagnosis was used. TreeAge Pro software (TreeAge Software, Williamston, MA) was used for the design and analysis of this model.

Sensitivity and specificity of the screening tests and probabilities of Down syndrome, patients' decision to proceed with amniocentesis after a positive test, patients' decision to terminate a pregnancy, and risk of procedure-related loss were all obtained from the FASTER trial.[6] To obtain costs and utilities for the outcomes related to Down syndrome screening and the screening tests themselves, the English literature was searched for the following terms: nuchal translucency, aneuploidy, serum screen, Down syndrome, biochemical screen, obstetric ultrasound, MSAFP, PAPP-A, free β, amniocentesis, and genetic screening. Of the articles obtained from this literature search, the lists of references were searched to make sure no other references were missed.

The sensitivities used for the screening regimens ranged from 69% for the Triple Screen to 95% for the fully Integrated first- and second-trimester screens at a 5% false-positive rate (Table 1). A range of cutoffs are applicable to these false-positive rates. For first-trimester combined screening it is equivalent to an approx-

Table 1. Input Variables in the Base-Case Analysis

Variable	Probability from FASTER
First trimester risk of Down syndrome	0.002419 (92/38,033)
Second trimester risk of Down syndrome	0.002497 (88/35,236)
Third trimester risk of Down syndrome	0.002185 (77/35,236)
Proportion of Down syndrome surviving to live birth	0.7027 (26/37)
Proportion of women who obtained second trimester screening	87.9% overall 92.8% of first trimester screens
Sensitivity of nuchal translucency plus serum screen	0.85 (0.80–0.90)
False-positive rate of nuchal translucency	0.05 (0.026–0.095)
Sensitivity of second trimester Triple Screen	0.69 (0.61–0.80)
False-positive rate of second trimester Triple Screen	0.05 (0.03–0.097)
Sensitivity of second trimester Quad Screen	0.81 (0.74–0.90)
False-positive rate of second trimester Quad Screen	0.05 (0.03–0.119)
Sensitivity of Serum Integrated Screen	0.86 (0.81–0.90
False-positive rate of Serum Integrated Screen	0.05 (0.03–0.081)
Sensitivity of Fully Integrated Screen	0.95 (0.90–0.95)
False-positive rate of Fully Integrated Screen	0.05 (0.017–0.05)
Sensitivity of Contingent Screen	0.93
False-positive rate of Contingent Screen	0.043
Sensitivity of Sequential Screen	0.95 (0.91–0.97)
False-positive rate of Sequential Screen	0.049 (0.02–0.098)
Proportion of Women receiving nuchal translucency where appropriates images failed to be obtained or were subsequently rejected at (wk)	
10	3.1% fail, 7.4% rejected
11	2.6% fail, 3.1% rejected
12	3.2% fail, 2.3% rejected
13	5.5% fail, 2.9% rejected
Accept amniocentesis with screen positive	0.571, Range (0.33–0.90)
Younger than age 35 y	0.518
Age 35 y or older	0.616
Loss from amniocentesis	1 in 1,600=0.0006, Range (1 in 200 to 1 in 1,600)
Proportion of women with Down syndrome who terminated pregnancy	51 in 52=0.981, Range (0.4–1.0)

FASTER, First and Second Trimester Evaluation of Risk.

imate cutoff of 1 in 250; for second-trimester triple and quad screening it approximates a cutoff of 1 in 140; for integrated and sequential screening it is a cutoff of approximately 1 in 270. For contingent screening, cutoffs used in the first trimester were 1 in 30 and 1 in 1,500 and for the second trimester were 1 in 270.

Overall, the proportion of women who would obtain an amniocentesis with a positive test was 57%, whereas the proportion who terminated a Down syndrome pregnancy was 98%. To capture behavior that would vary between different populations, these values were varied over wide ranges (Table 1). The rate of Down syndrome in the study population was higher than that seen in the general population at 0.0024,[13] and the loss rate from amniocentesis was lower than that commonly quoted[14] at 1 in 1,600. However, this value was varied to as high as 1 in 200 in the sensitivity analysis. The trimester-specific Down syndrome risks were used to modify the number of Down syndrome cases that would be identified during each trimester, and eventually the number of Down syndrome children born in each arm of the analytic model.

The costs of these outcomes and of the testing itself are estimates from the existing literature. All historical costs are inflated using the medical component of the consumer price index to the year 2006 dollars. All costs and benefits were discounted at a rate of 3%.[15] Specifically, the outcomes of procedure-related loss and Down syndrome were used in the cost–utility analysis. The costs[10,12,16,17] (Table 2 and Table 3) used in this analysis were $146 for first-trimester screening, $66 for the second-trimester Triple Screen, and $86 for a second-trimester Quad Screen. A consultation with a genetic counselor is estimated at $68, and if a diagnostic procedure is also done, the total cost is $1,308.[18,19] Terminations of pregnancy done in the first and second trimester are $648 and $1,146, respectively.[20] The societal cost of raising and caring for an individual with Down syn-

Table 2. Costs Used in Base-Case Analysis

Variable	Cost (Adjusted to 2006 $*)	Range
Nuchal translucency plus first trimester SS	$146.32	($100–300)
Second trimester Triple Screen	$66.41	($50–150)
Second trimester Quad Screen	$85.54	($50–150)
Genetic counselor consultation (1 h)	$67.90	($50–100)
Amniocentesis (includes genetics consult)	$1,307.84	($500–2,000)
First trimester pregnancy termination	$648.29	($350–1,200)
Second trimester termination	$1,145.77	($540–1,620)
Cost of Down syndrome	$762,748	($600,000–800,000)

SS, Stepwise Sequential.
* All costs inflated to 2006 dollars using medical consumer price index.

Table 3. Utilities Used in Base-Case Analysis

Variable	Utility	Range
Utility of uncomplicated pregnancy	1.0	
Utility of positive screening test	0.96	(0.93–0.99)
Utility of procedure-related miscarriage	0.93	(0.89–0.97)
Utility of pregnancy termination	0.91	(0.86–0.96)
Utility of Down syndrome live birth	0.81	(0.75–0.87)

drome is $762,748.[21,22] This cost was only applied to Down syndrome children born.

To estimate the effect of the outcomes of procedure-related loss and Down syndrome, utility, a metric commonly used in cost-effectiveness analyses, was incorporated. Utility is a measure of the happiness (or unhappiness) generated from various outcomes. It is reported on a scale from 0 (death) to 1 (perfect health). The utilities used were previously measured by the standard gamble metric and were 0.93 for a procedure-related loss and 0.81 for the birth of a Down syndrome child and come from a single study of women's preferences toward prenatal diagnostic outcomes.[23,24] The utilities of the different outcomes were factored into the discounted life expectancies to generate quality-adjusted life years per standard techniques.[25] The utility for Down syndrome was multiplied times the life expectancy, discounted at 3% to determine the decrease in quality-adjusted life years. The utility for a false-positive test was multiplied times a half-year discounted period to determine quality-adjusted life years lost. The utility decrement for any type of pregnancy loss, including a pregnancy termination, was applied over a 2-year discounted period to determine quality-adjusted life years lost.

The analyses were run to obtain total costs, costs per Down syndrome diagnosed, and cost–utility ratios incrementally comparing the seven strategies. Strategies that were dominated, that is they cost more and led to worse outcomes than any other strategy, were eliminated from the incremental comparisons. For cost- or quality-adjusted life year ratio, values less than $100,000 per quality-adjusted life year were considered cost-effective.[25]

Several sensitivity analyses were then performed. Univariable analysis was performed first, varying different inputs of the model. The Down syndrome screens' sensitivities and false-positive rates were varied over ranges achieved in the FASTER trial. The rate of procedure-related losses was varied up to a loss rate of 1 in 200. The acceptance of amniocentesis and that of a termination of pregnancy were also varied over possible ranges. To examine the sensitivities and specificities achieved by first-trimester screening at 11, 12, and 13 weeks of gestation, the inputs were varied over the 3 weeks as well. When the ranges of outputs crossed above or below the different thresholds of cost-effectiveness, a threshold analysis was performed to find the input value that would just equal the threshold value for the output. After univariable analyses were performed, a Monte Carlo simulation was performed, which varied all of the input distributions of the model simultaneously. To examine the Stepwise Sequential screening strategy further, the false-positive rates of 2%, 5%, and 10%, with associated sensitivities, were examined separately within the model.

RESULTS

In the 38,033 women evaluated in the FASTER trial, the Contingent Sequential dominated (lower costs, better outcomes) all other screens (Table 4). For example, the Contingent Sequential Screen cost 32.3 million dollars while the other screens ranged from 32.8 to 37.5 million dollars. The Sequential strategy led to the identification of the most Down syndrome fetuses of all of the screens, but at a higher cost per Down syndrome case diagnosed ($719,675 compared with $690,427) as compared with the Contingent Sequential. Because of the lower overall false-positive

Table 4. Costs and Cost–Utility Analysis of Down Syndrome Screening Strategies

Screen Method	Costs in Millions of 2006 $	QALY	Incremental Cost–Utility Ratio Compared With Quad Screen
Triple Screen	37.5		Dominated
Quad	32.8	980,774	
Combined first	35.2	980,777	$500,560/QALY
Integrated	34.5	980,820	$33,385/QALY
Serum Integrated	33.6	980,790	$42,188/QALY
Stepwise Sequential	34.4	980,823	$29,524/QALY
Contingent Sequential	32.3	980,832	Dominant

QALY, quality-adjusted life years; Dominated, costs more with worse outcomes; Dominant, costs less with better outcomes.

rate leading to fewer procedure-related miscarriages, the Contingent Sequential resulted in the highest quality-adjusted life years as well.

In the sensitivity analysis, when the rate of amniocentesis after a positive screening test was varied from 33% to 90%, there was no difference in the ranking of the screening strategies. Of note, with an amniocentesis rate of 0.473 and below, the Quad Screen was no longer dominated by the Contingent Screen. However, the Contingent Screen remained cost-effective at $832 per quality-adjusted life year at this amniocentesis rate and increased to $18,381 per quality-adjusted life year at the amniocentesis rate of 0.33. When the rate of termination of a Down syndrome fetus was varied from 40% to 100%, the model remained robust. At a termination rate of just below 80%, the Quad Screen became cheaper than the Contingent Sequential. Again, the Contingent Sequential remained cost-effective between termination rates from 40% to 100% at $20,772 per quality-adjusted life year at a termination rate of 40%, $8,925 per quality-adjusted life year at a termination rate of 60%, and being cheaper at 80% to 100%. When the procedure-related miscarriage rate was varied to as high as 1 in 200, there was no difference in the cost-effectiveness ranking of the screening strategies, with the Contingent Sequential program dominating the other strategies.

To address the variance of the screening characteristics of first-trimester screening, models were created and analyzed at 11, 12, and 13 weeks of gestation. This sensitivity analysis is fundamentally similar to varying the sensitivity and false-positive rates of each of the screening tests. Similar to that sensitivity analysis, at each given week the Contingent Sequential was dominant, as it had been in the baseline analysis. Further, the robustness of the model persisted with sensitivity analysis of the costs and utilities used in the model when they were varied over theoretical ranges. Finally, a Monte Carlo simulation examined the model by varying the various inputs simultaneously over their respective distributions over 38,033 trials. Again, the Contingent Sequential led to the lowest costs and best outcomes ($P<.001$).

Finally, when the false-positive rate of the Sequential screening test was varied from 2% to 10%, the Contingent Sequential no longer dominated. In this sensitivity analysis, the 2% false-positive (1% at each step) and 10% false-positive (5% at each step) Sequential models were added to the analysis, and three of the strategies that had been dominated, triple Screen, first-trimester screen, and the integrated screen, were eliminated. The 2% false-positive (34.6 million dollars) and 10% false-positive (35.2 million dollars) Sequential strategies were both more expensive than the Contingent Sequential. However, the 2% false-positive Sequential led to slightly better outcomes and was marginally cost-effective as compared with Contingent Sequential, at $45,206 per quality-adjusted life year. The 2% false-positive Sequential remained marginally cost-effective as compared with the Contingent Sequential while varying the amniocentesis rate, the termination rate, the procedure-related miscarriage rate, and the costs and utilities used in the models.

DISCUSSION

It is clear that in the United Kingdom, where first-trimester screening was first used on a large scale, it has become the de facto standard of care. The frequency of use of this screening strategy has accelerated in the United States, and is increasingly available clinically and can be anticipated to soon replace the current standard of care.[26] Thanks to multiple large population-based studies there is evidence to support this based on efficacy.[3–6] However, with the financial limitations inherent in any healthcare system it is our responsibility to sift from the myriad different strategies the ones that are most cost-effective as well as acceptable to patients.

First-trimester screening does have great appeal to patients and their families. It allows earlier reassurance if the results return normal, as they will in the vast majority of cases. If the results are abnormal, aneuploidy can be confirmed much earlier and pregnancy termination completed in the first trimester. Also data from several studies suggest that use of the first-trimester results together with second-trimester serum screening can increase the detection rate for a given test-positive rate. It is therefore reassuring that our analysis documents that the Stepwise and Contingent are both cost-effective when compared with second-trimester screening strategies alone. Comparing the two, Contingent dominates as it is anticipated that only a small proportion of patients would proceed to second-trimester screening with a minimal drop in detection rate. However, by lowering the Stepwise false-positive rate to 2%, an improvement in overall outcomes is achieved because of the fewer procedure-related miscarriages and need for invasive testing. This improvement, which is small as compared with Contingent, comes at a cost of more than $45,000 per quality-adjusted life year. This increased cost to society, which is due both to the cost of screening all women in the second trimester and the small number of Down syndrome cases missed as compared with Contingent, is cost-effective, but only marginally so. Given that these two options are very close in both costs and outcomes, it may be that a compromise option which lowers the false-positive rate of the Contingent Screen may ultimately be the most cost-effective option. Further, as in all strategies, their performance depends on the patients' compliance in completing the screening process as indicated.

The current standard of care based on the American College of Obstetricians and Gynecologists most recent Guidelines for Perinatal Care,[27] the Triple Screen, has been superseded, based both on detection rate and cost-effectiveness. This should be an impetus to the umbrella organizations to accelerate the creation of new guidelines. This is particularly the case because one of the strategies that is more cost-effective than the Triple Screen, based on our data, is the Quad Screen. Importantly, this screening strategy does not require special training of practitioners and can be performed at centralized laboratories at the same gestational age as the Triple Screen is now. This makes it much more easily applicable to the general population across the country, including in areas where specialized ultrasound services may not be available. It also can be incorporated without a need for change in the timing routine of prenatal visits. Thus, it would seem that a reasonable approach toward population screening would be to immediately expand second-trimester screening by offering Quad screening as a population-wide strategy in which quality control would be easily achieved through centralized laboratories similar to the California State AFP program. However, because the Contingent and Sequential 2% false-positive screens lead to improved sensitivity over the Quad Screen at lower societal costs, the long-term strategy needs to include access to first-trimester screening for all patients.

Expanding access to first-trimester screening, particularly the nuchal translucency ultrasonography, will be the most challenging aspect of improving the national standard. It has been repeatedly documented that quality control issues are most challenging with the ultrasonographic component of first-trimester screening, the nuchal translucency measurement. To this end the Fetal Medicine Foundation and the Society for Maternal–Fetal Medicine both have nuchal translucency credentialing programs. In those areas where credentialed practitioners are available, the Contingent Screen would most likely offer the best balance of detection rate and cost-effectiveness and has maximal appeal to patients and their care providers. Of note, although we found that the contingent screening strategy seems to be the most cost-effective from a societal standpoint, individuals are likely to have specific preferences which differ from society as a whole. To those individuals, it might be best to use a screening strategy that maximizes sensitivity, minimizes the false-positive rate, or skips over screening altogether to obtain a diagnosis.

Our study is not without limitations. We used the sensitivities demonstrated by the FASTER trial. It is possible that a national screening program will not be able to achieve sensitivities this high. However, because each of the combination first- and second-trimester screens that were the best included nuchal translucency, the test characteristics would change in a similar fashion, thus should not change the ranking of the cost-effectiveness of such programs. Further, we used estimates of societal costs rather than those faced by the patients. Because patients face the up-front costs of screening if they do not have insurance coverage and generally don't bear the high medical costs of having a child with Down syndrome, they may choose to forgo such screening rather than pay out of pocket. Using such societal costs is the standard in cost-effectiveness analyses and points the way toward the best use of resources. Thus, to encourage the most

cost-effective use of Down syndrome screening, societal coverage of these screening tests either through health care insurance or large, centralized screening programs should be implemented. Of note, we did not incorporate the cost of nuchal translucency quality assurance programs into our analysis, because data for cost is not readily available. Although this potential cost increase could strengthen the position of "serum only" strategies, relative to the costs of nuchal translucency screening, such programs are likely to add only a small percentage increase. Of note, we also used a loss rate due to amniocentesis that was lower than generally quoted in the broader literature. This was the loss rate seen in the FASTER trial; to ensure the robustness of our model, we did vary this rate to as high as 1 in 200 without a significant change in the ordering of the outcomes. Finally, the various other inputs used in the analysis are based on the existing literature and may not represent every geographic region of the country. However, to address this, we conducted sensitivity analyses, varying each of the inputs and found consistency in the outcomes of our models including the Monte Carlo simulation.

It is critical to develop a cohesive national strategy regarding prenatal screening and diagnosis. Without this the uncontrolled proliferation and marketing of first- and second-trimester strategies or combinations thereof will not only make a priori genetic counseling regarding choices complex, but also make discussion of results a nightmare for patients and counselors. We hope that these data will give direction regarding the best use of the new strategies that are available, all of which are better than what patients have experienced in the past.

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APPENDIX

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