THE GENETIC SONOGRAM

Jude P. Crino, M.D.

JOHNS HOPKINS MEDICINE
JOHNS HOPKINS HEALTH SYSTEM

Gynecology and Obstetrics

SCREENING PRINCIPLES

EVALUATION OF TESTS KEY MEASURES

- Sensitivity – proportion of people with the disease who test positive (aka detection rate)
- Specificity – proportion of people without the disease who test negative
- Positive Predictive Value – proportion of people with a positive test who have the disease
- Negative Predictive Value – proportion of people with a negative test who do not have the disease

EVALUATION OF TESTS

		DISEASE +	DISEASE -
TEST	+	A (true positive)	B (false positive)
	-	C (false negative)	D (true negative)

Sensitivity A/A+C
Specificity D/B+D
Positive Predictive Value A/A+B
Negative Predictive Value D/C+D

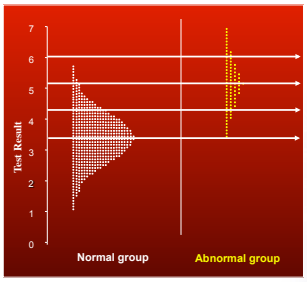
SCREENING PRINCIPLES PREDICTIVE VALUE

- Predictive value varies with prevalence
  - with increasing prevalence:
    - positive predictive value increases
    - negative predictive value decreases
  - at low prevalence, positive predictive value will be low and negative predictive value will be high *regardless of how good the test is*

SCREENING PRINCIPLES SENSITIVITY AND SPECIFICITY

- Sensitivity and specificity do not vary with prevalence
- Sensitivity varies with the threshold value (cutoff) for a positive test
- Specificity and positive predictive value vary with sensitivity
  - with increasing sensitivity, specificity and positive predictive value decrease

SCREENING PRINCIPLES CUTOFF



Normal (%) FPR	Abnormal (%) Sensitivity
0%	20%
3%	50%
10%	80%
50%	100%

Courtesy Kypros Nicolaides, M.D.

SCREENING PRINCIPLES FALSE POSITIVE RATE

- False positive rate varies with sensitivity
  - with increasing sensitivity, false positive rate increases
- At low prevalence, false positive and screen positive rates are approximately equal
- To compare different screening tests for the same population, either the false positive rate or the sensitivity must be fixed

EXAMPLE
Second Trimester Triple Screen
DS Prevalence 0.125% (1/800)

		DISEASE +	DISEASE -
TEST	+	6	300
	-	4	7690

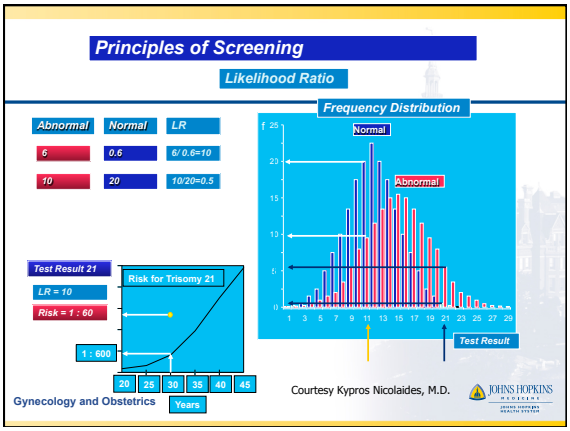
Sensitivity 6/10 = 60%
Specificity 7690/7990 = 96%

Positive Predictive Value 6/306 = 2%
Negative Predictive Value 7690/7694 = ~100%

False Positive Rate 300/8000 = 3.8%

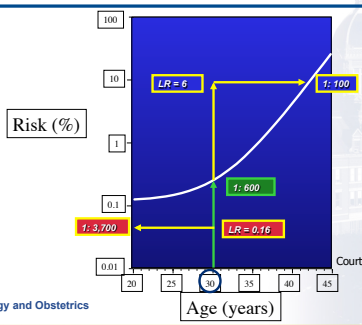
SCREENING PRINCIPLES LIKELIHOOD RATIO

- Frequency of abnormal / frequency of normal at a given test result
- Used to calculate patient-specific risk based upon:
  - patient's individual test result
  - population distribution of test results



Courtesy Kypros Nicolaides, M.D.

CALCULATION OF PATIENT-SPECIFIC RISK



Courtesy Kypros Nicolaides, M.D.

FIRST TRIMESTER SCREENING

FIRST TRIMESTER COMBINED SCREEN

- First trimester combination of NT and serum biochemistry is a very effective screen for Down syndrome (and other aneuploidy) in the general population (DR ~85% @ 5% FPR)
- Down syndrome screening in singletons based on NT alone (DR ~75% @ 5% FPR) is less effective than NT plus biochemistry
- Use of additional sonographic markers with the combined screen improves test performance (increased sensitivity, lower screen positive rate)

FIRST AND SECOND TRIMESTER SCREENING

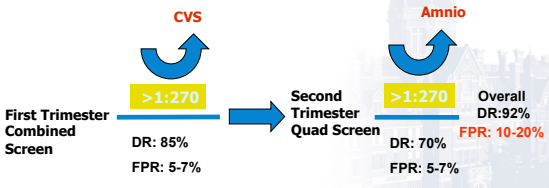
INTEGRATED SCREEN

- 1st and 2nd trimester risk estimates combined to give single risk
  - 2-step screen / 1 result
- Maternal age & gestational age included
- Serum integrated (1st trim PAPP-A + 2nd trim quad), DR 85-88% at 5% FPR
- Fully integrated (1st trim NT/PAPP-A + 2nd trim quad), DR 94-96% at 5% FPR

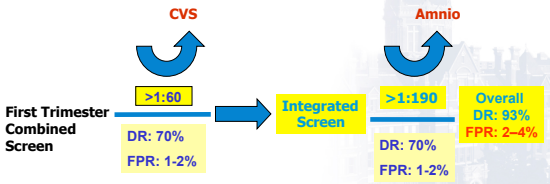
SEQUENTIAL SCREEN

- 2 step screen, 2 risk results
- 11-14 weeks NT + biochem
- Results provided, CVS if ↑ risk
- 15+ weeks quad screen
- *False positive rates are additive*

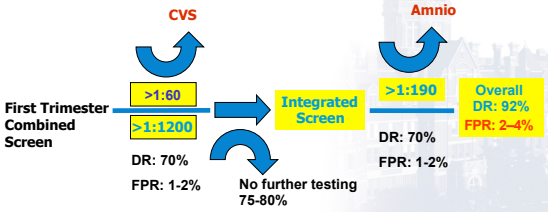
INDEPENDENT SEQUENTIAL SCREEN



STEPWISE SEQUENTIAL SCREEN



CONTINGENT SEQUENTIAL SCREEN



DOWN SYNDROME SCREENING (FPR 5%)

		Detection Rate (%)
1st Trimester	NT Ultrasound	64-70
1st Trimester	1st Trimester Blood Screen → NT Ultrasound	82-87
2nd Trimester	Triple Screen	69
2nd Trimester	Quadruple Screen	81
Integrated Screen	1st Trimester Blood Screen → NT Ultrasound → 2nd Trimester Blood Screen	94-96
Serum Integrated	1st Trimester Blood Screen → 2nd Trimester Blood Screen	85-88

ACOG Practice Bulletin No. 77, January 2007

THE GENETIC SONOGRAM

BASIC PRINCIPLES

- Distinction between structural anomaly and a “marker”
- Ultrasound markers are “evolving”
- Predictive value varies with prevalence
- Most studies are in high risk patients

“GENETIC SONOGRAM”

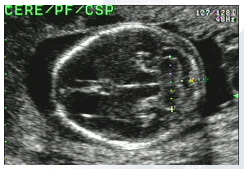
- Application of second trimester (14-24 w) sonography to adjust fetal aneuploidy risk
- Standardized, systematic approach
  - Complete anatomic survey
  - Markers of fetal aneuploidy
- Correlation with other risk factors
  - Maternal age, obstetric or family history, maternal serum testing results

MARKERS OF FETAL ANEUPLOIDY

- Thickened nuchal fold
- Short femur/ humerus
- Renal pelvis dilation
- Echogenic intracardiac focus
- Echogenic bowel
- Cerebral ventriculomegaly
- Absent or hypoplastic nasal bone
- Aberrant right subclavian artery

THICKENED NUCHAL FOLD

- Transverse, "off-axial" view through post fossa
  - include cisterna magna, cerebellum
- Outer occipital bone - outer skin edge
- Cutoff 5 or 6 mm



THICKENED NUCHAL FOLD

Table 1. Likelihood ratios for Down syndrome according to biparietal diameter and nuchal fold thickness measurements

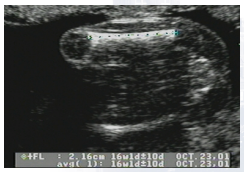
Observed biparietal diameter (mm)	Gestational age* (wk)	Expected nuchal fold thickness (mm)	Observed nuchal fold thickness						
			1-1.9 mm	2-2.9 mm	3-3.9 mm	4-4.9 mm	5-5.9 mm	6-6.9 mm	≥7 mm
28	14.6	2.42	0.41	0.44	0.72	2.75	17.78		
30	15.2	2.58	0.40	0.43	0.63	2.11	13.02		
32	15.7	2.74	0.40	0.42	0.57	1.64	9.57		
34	16.2	2.90	0.40	0.42	0.52	1.30	7.06		
36	16.8	3.06	0.40	0.41	0.49	1.05	5.23		
38	17.3	3.22	0.40	0.41	0.46	0.87	3.91	26.33	
40	17.9	3.38	0.40	0.41	0.45	0.74	2.95	19.23	
42	18.4	3.54	0.40	0.40	0.43	0.65	2.25	14.07	
44	19.0	3.70	0.40	0.40	0.42	0.58	1.74	10.33	
46	19.5	3.86	0.40	0.40	0.42	0.53	1.38	7.61	
48	20.1	4.02	0.40	0.40	0.41	0.50	1.11	5.64	
50	20.6	4.18	0.40	0.40	0.41	0.47	0.91	4.20	28.49
52	21.1	4.34	0.40	0.40	0.41	0.45	0.77	3.16	20.80
54	21.7	4.50	0.40	0.40	0.40	0.44	0.67	2.40	15.21
56	22.2	4.66	0.40	0.40	0.40	0.43	0.60	1.86	11.16
58	22.8	4.82	0.40	0.40	0.40	0.42	0.54	1.46	8.21
60	23.3	4.98	0.40	0.40	0.40	0.41	0.50	1.17	6.07

*Gestational age estimates are based on biparietal diameters.

AJOG 2000;182:192

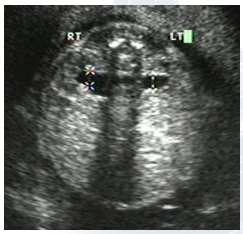
SHORT FEMUR/ HUMERUS

- Expected values based on BPD in normal controls
- Standard measurement of bone length
- Measured to expected ratio
  - cutoffs 0.89-0.93



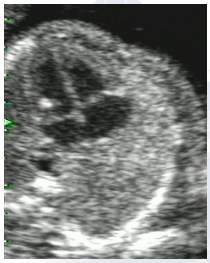
RENAL PELVIS DILATION

- Transverse image of renal pelvis
- A-P measurement of pelvic diameter
- Cutoff 3, 4 or 5 mm



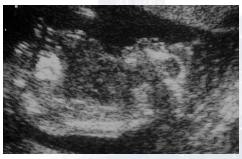
ECHOGENIC INTRACARDIAC FOCUS

- Calcified papillary muscle
- Discrete, bright focus within ventricle
- Usually left, may be right or bilateral
- Technique may affect prevalence



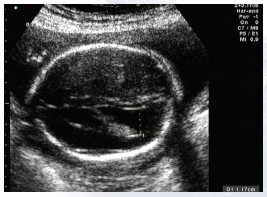
ECHOGENIC BOWEL

- Grading system for echogenicity
- Risk increases with brightness
- Sens for DS 12-13% at 1.4% FP
- Infection, CF, swallowed blood
- 50-75% normal



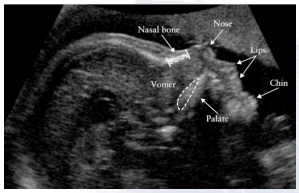
CEREBRAL VENTRICULOMEGALY

- Transverse, transventricular plane
- Internal diameter of distal atrium measured perpendicular to ventricular cavity at glomus of choroid plexus
- Cutoff 10 mm



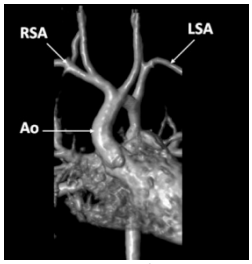
ABSENT/ HYPOPLASTIC NASAL BONE

- Fetal profile in mid-sagittal plane
  - Nose, lips, chin, palate
- Length of nasal bone measured
- Cutoff varies between studies

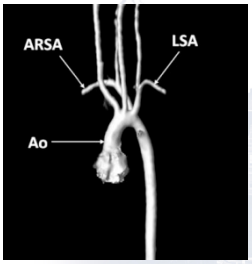


Ultrasound Obstet Gynecol 2010;36:285

ABERRANT RIGHT SUBCLAVIAN ARTERY



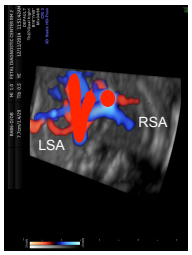
normal



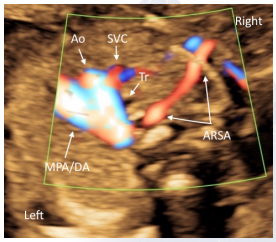
aberrant right subclavian artery

Ultrasound Obstet Gynecol 2010;36:548

ABERRANT RIGHT SUBCLAVIAN ARTERY



normal



aberrant right subclavian artery

Courtesy Julia Solomon, M.D.

MULTIPLE MARKER SCREENING Risk Assessment Models

- Any marker present
- Index Scoring System
- Application of likelihood ratios
  - Combining positive LR of any identified marker, risk reduction only if no marker identified (AAURA)
  - Combining positive LR of any identified marker and negative LR of absent markers

INDEX SCORING SYSTEM

FINDING	SCORE
Major anomaly	2
Nuchal fold ≥ 6mm	2
Short femur (M:E ≤ 0.91)	1
Short humerus (M:E ≤ 0.90)	1
Renal pelvis dilation ≥ 4mm	1
Hyperechoic bowel	1
Echogenic intracardiac focus	1

INDEX SCORING SYSTEM

MATERNAL AGE	SCORE
< 35	0
≥ 35 and < 40	1
≥ 40	2

AAURA

Age
Adjusted
Ultrasound
Risk
Assessment

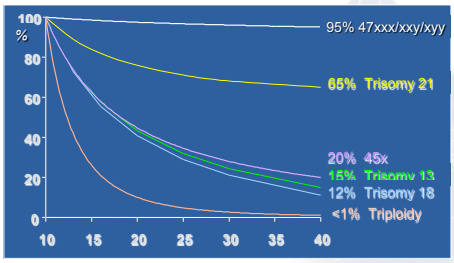
AAURA

MA RISK X EGA RISK X LR

LR = likelihood ratio (sens/false pos)

Assessment of Risk

Gestational age



AAURA

FINDING	LIKELIHOOD RATIO DS
Structural defect	25
Nuchal fold > 5mm	18.6
Echogenic bowel	5.5
Short humerus (M:E ≤ 0.89)	2.5

AAURA

FINDING	LIKELIHOOD RATIO DS
Short femur (M:E ≤ 0.91)	2.2
Echogenic intracardiac focus	2
Renal pelvis dilation > 3mm	1.6
Normal ultrasound scan	0.4

Ultrasound Ob Gyn 1998

Age Adjusted Ultrasound Risk Assessment (AAURA)

FOR DOWN SYNDROME

by David A. Nyberg, MD
Instructions: Fill in yellow spaces
Blue spaces may be modified

Name	Jane Doe
Age	34
Date	06/13/1992
LMP	04/14/1992
LMP age	17.5
Biparietal diameter (BPD)	
Femur Length (FL)	2.3
Humerus length (HL)	2.4
Nuchal fold (mm)	4
Renal pelvis (mm)	2
Echogenic bowel (yes.ho)	no
Echogenic intracardiac focus (yes.ho)	no
Major anomaly (cardiac etc) (yes.ho)	no
(may list here)	
other (optional)	
Apriori risk based on Age (1:__)	342
Apriori risk based on biochemistry (if known, otherwise make blank)	507
Ultrasound Risk (1: __)	**833**
Benacerraf Scoring Index	**0**

ASSUMPTIONS

Question	POSITIVE ?	THRESHOLD (in mm)	Risk Factor if positive (as isolated finding)	Scoring Index if Positive
Short FL?	NO	2.27	1.5	1
Short HL?	NO	2.18	5	1
Nuchal thickness?	NO	5	11	2
Pyelectasis?	NO	3	1.5	1
Echogenic bowel?	NO		6.7	1
Echogenic chorda tendi	NO		1.8	1
Major defect?	NO		25	2
Age factor				

Recommend Amniocentesis?

Total Benacerraf Score:

(yes if risk exceeds amnio threshold stated to left and below)

(yes if score 2 or greater)

Assumptions:		
Amniocentesis Threshold (1:__)	200	default
Apriori risk of Down syndrome (Second Trimester or Term)	Second Trimester	
Reduction of Risk if normal US	40%	

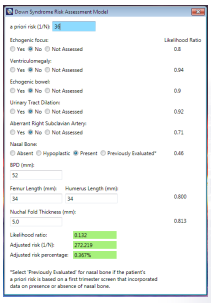
200

Second Trimester Term

Provided courtesy of David A. Nyberg, MD

Meta-analysis of second-trimester markers for trisomy 21

M. AGATHOKLEOUS*, P. CHAVEEVA*, L. C. Y. POON*, P. KOSINSKI* and K. H. NICOLAIDES*†



ROLE OF GENETIC SONOGRAM AFTER PREVIOUS SCREENING

- May increase detection rate and/or decrease screen positive rate for patients with borderline results
- Does not have the power to change screen positive to negative if *a priori* risk sufficiently high
- Negative sonographic result may be falsely reassuring

ROLE OF GENETIC SONOGRAM AFTER PREVIOUS SCREENING

Table 2. Comparison of the Screening Protocols

Parameter	Sequential	Sequential + Genetic Sonogram
DR, n/N (%)	15/17 (88.2)	14/17 (82.4)
FPR, n/N (%)	390/6269 (6.2)	266/6269 (4.2)
PPV, %	3.7	5.0
OAPR, 1/x	25.9	18.8
AUC	0.944	0.953

AUC indicates area under the receiver operating characteristic curve; DR, detection rate; FPR, false-positive rate; n/N, number of Down syndrome cases detected/total number of Down syndrome cases; OAPR, odds of an affected pregnancy given a positive result; and PPV, positive predictive value.

J Ultrasound Med 2013;32:1607

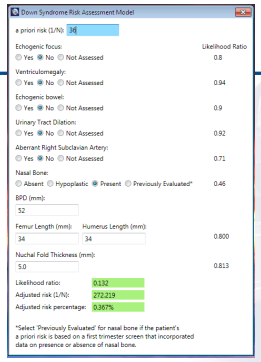
ROLE OF GENETIC SONOGRAM AFTER PREVIOUS SCREENING

Table 3. Detection Rate for a 5% False-Positive Rate With Standard Screening Policies and With Risk Modified by Genetic Sonogram Result

Policy	Standard	After Sonogram
Combined	81	90*
Quadruple	81	90
Integrated	93	98
Stepwise	97	98
Contingent	95	97
Stepwise sonogram†	–	90
Contingent sonogram†	–	90

Data are %.
* Not interpreting the test until the sonogram is complete.
† Replacing the second-stage quadruple markers with the sonogram.

Obstet Gynecol 2009;114:1189

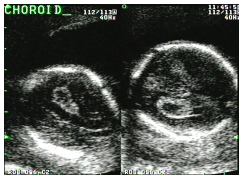


THE GENETIC SONOGRAM
Limitations and unresolved issues

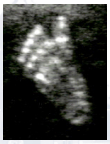
- Some markers are not independent
  - Femur and humerus lengths, nasal bone in first and second trimesters
- Incidence of some markers varies with ethnicity
  - Echogenic intracardiac focus, nasal bone
- Various cutoffs used in different studies
- Counseling for isolated minor marker in low risk patient

OTHER SONOGRAPHIC MARKERS

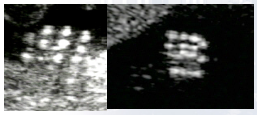
CHOROID PLEXUS CYST



SANDAL TOE



HYPOPLASTIC 5TH MID PHALANX



OTHER SONOGRAPHIC MARKERS

- Choroid plexus cyst
- Abnormal skull shape
- Wide iliac wing angle
- Hypoplastic 5th mid phalanx/ clinodactyly 5th finger
- Sandal gap
- Single umbilical artery
- Chorioamniotic separation

"The theory that a greater number of fetuses with trisomy 21 could be identified in the low risk patient group, combined with the fear of missing an affected fetus if every minor marker is not reported, has fostered over-diagnosis and excessive counseling."

- Beryl Benacerraf, 2000

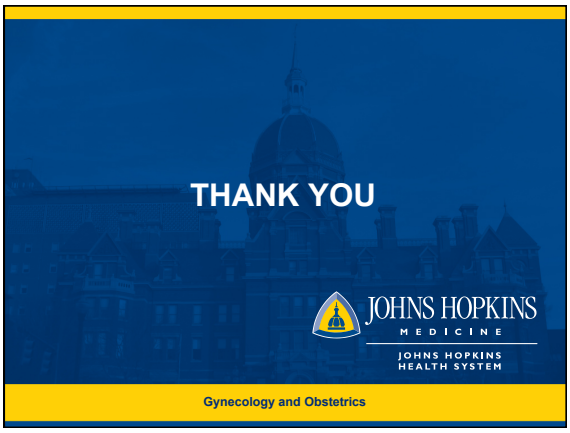
GUEST EDITORIAL

Obstetrical Sonography:
The Best Way to Terrify a Pregnant Woman

The researchers who originally described these findings did so in women at high risk to have a fetus with the Down syndrome.[65-66] These were pregnant women older than 35 years or who had a positive "triple marker" screening test for the Down syndrome. In this group of women the application of these findings increases the probability of finding Down syndrome fetuses, and they perform admirably in this regard. However, these women have already been counseled that amniocentesis is appropriate in their case. They are having a sonogram in order to *downgrade* their risk to a level where they may appropriately forgo amniocentesis.[38,64-71] When examining a mother-to-be in this circumstance, I fully recognize the value of identifying these "abnormalities" and can counsel these women appropriately that their already substantial risk is further increased if I find one or more of these features. More importantly to her, if no markers for the Down syndrome are found, her level of risk may be significantly reduced.[64-66]

But then investigators (with the best of intentions, I am certain) appear to have taken a misstep. These findings, when seen in a woman with a low risk of having a Down syndrome fetus, were used to *upgrade* her risk.[40,72] The consumers of this information, the physicians in the trenches, read these scientific papers and then identify these "abnormalities" during a routine sonogram. What are they to tell the patient? This woman hasn't already been counseled. She is having a sonogram for "reassurance" (forget that now). Her husband, children, and parents are with her. There is a party atmosphere. The videotape is rolling. Soon the giggling and finger pointing at the screen will cease. The questions will change abruptly from "is that the heartbeat?" or "is that the penis there?" to "are you saying that my child is going to be mentally retarded?"

J Ultrasound Med 2000;19:1


THANK YOU
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