

# The Infertility Workup 2011

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# Outline:

- \* Review basic infertility textbook workup; compare and contrast to current ASRM guidelines.
- \* Spotlight on the Thyroid gland.
- \* Ovarian reserve testing and AMH as an early warning system.
- \* Extended preconception screening; the new paradigm.



Who?

**Table 1. Cumulative Probability of Pregnancy in Normally Fertile Couples**

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<b>MONTH</b>	<b>MONTHLY PROBABILITY OF PREGNANCY</b>	<b>CUMULATIVE PROBABILITY OF PREGNANCY</b>
1	0.2	0.20
2	0.2	0.36
3	0.2	0.49
4	0.2	0.59
5	0.2	0.67
6	0.2	0.74
7	0.2	0.79
8	0.2	0.83
9	0.2	0.86
10	0.2	0.89
11	0.2	0.91
12	0.2	0.93

- \* After one (1) year, 7% risk of a type 1 error
- \* Given that a measurable decline in fertility is demonstrable by age 35, 6 months if  $\geq 35$ .
- \* No reason to wait for evaluation if obvious oligoanovulation / amenorrhea, other obvious risk factors apparent.
- \* Prevalence of infertility approximately 30%
- \* Only  $\frac{1}{2}$  of those with primary infertility seek infertility services but only  $\frac{1}{4}$  of those with secondary infertility

# Textbook Evaluation:

1. Male factor (SA)
2. Ovulatory and luteal function (endometrial biopsy or serum progesterone).
3. Cervical factor (PCT)
4. Uterine factor (HSG and/or hysteroscopy; ultrasound)
5. Tubal factor (HSG and laparoscopy)
6. Endometriosis or other pelvic pathology (laparoscopy)

# 1. Optimal Evaluation of the Infertile Male

Best practice policy committee (ASRM & American Urological Association)

# Prevalence:

- \* 20% sole factor
- \* 30-40% contributing factor

# Reproductive History & Testing:

1. Coital frequency and timing
2. Duration
3. Childhood and developmental history
4. Medical/ surgery history
5. STD history
6. Toxin and heat exposure
7. SA: Properly performed x2 (at least 1 month apart), 2-5 days abstinence.

**Table II** Distribution of values, lower reference limits and their 95% CI for semen parameters from fertile men whose partners had a time-to-pregnancy of 12 months or less

	N	Centiles										
		2.5	(95% CI)	5	(95% CI)	10	25	50	75	90	95	97.5
Semen volume (ml)	1941	1.2	(1.0–1.3)	1.5	(1.4–1.7)	2	2.7	3.7	4.8	6	6.8	7.6
Sperm concentration ( $10^6$ /ml)	1859	9	(8–11)	15	(12–16)	22	41	73	116	169	213	259
Total number ( $10^6$ /Ejaculate)	1859	23	(18–29)	39	(33–46)	69	142	255	422	647	802	928
Total motility (PR + NP, %)*	1781	34	(33–37)	40	(38–42)	45	53	61	69	75	78	81
Progressive motility (PR, %)*	1780	28	(25–29)	32	(31–34)	39	47	55	62	69	72	75
Normal forms (%)	1851	3	(2.0–3.0)	4	(3.0–4.0)	5.5	9	15	24.5	36	44	48
Vitality (%)	428	53	(48–56)	58	(55–63)	64	72	79	84	88	91	92

\*PR, progressive motility (WHO, 1999 grades a + b); NP, non-progressive motility (WHO, 1999 grade c).

The values are from unweighted raw data. For a two-sided distribution the 2.5th and 97.5th centiles provide the reference limits; for a one-sided distribution the fifth centile provides the lower reference limit.

# First Semen Analysis at Outside Laboratories

Outside Laboratory			Overlake Reproductive Health		
Sperm Count	Motility	Morphology (Kruger)	Sperm Count	Motility	Morphology (Kruger)
36 million/ml	5%	14% normal	24 million/ml	50%	15% normal
8 million/ml	26%	---	15 million/ml	40%	15% normal
21 million/ml	49%	27% normal	5 million/ml	38%	15% normal
.01 million/ml	40%	---	12 million/ml	55%	16% normal
140 million/ml	40%	10% normal	60 million/ml	77%	21% normal
7 million/ml	55%	5% normal	17 million/ml	63%	15% normal

# Physical Examination:

- \* “A general physical examination is an integral part of the male infertility evaluation”.
- \* Severe Oligospermia /Azoospermia associated with increased prevalence of testicular cancer ( high risk age group 15-35).

# Other Tests:

- \* Endocrine evaluation?(FSH, T at a minimum; other tests? LH,E2,TSH,PRL?)
- \* Low volume (<1 cc), or no ejaculate: Post ejaculatory UA.
- \* Azoospermia, ?Oligospermia with low volume: Transrectal ultrasound (TRUS).

# Specialized Tests:

- \* Quantitation of leukocytes (not round cells)
- \* Antisperm antibodies
- \* Sperm viability tests

# Genetic Screening:

- \* Non-obstructive Azoospermia, Severe Oligospermia: Karyotype, y-micro deletion analysis.
- \* Obstructive Azoospermia: Assume that congenital bilateral absence of vas deferens = CFTR gene mutation and screen wife, offer genetic counseling.

# Optimal Evaluation of the Infertile Female

“Practice committee of ASRM”

# History:

- \* Relevant history includes 1) gravidity, parity, pregnancy outcome, and associated complications, 2) age at menarche, cycle length and characteristics, and onset/severity of dysmenorrhea, 3) methods of contraception and coital frequency, 4) duration of infertility and results of any previous evaluation and treatment, 5) past surgery, its indications and outcome, previous hospitalizations, serious illnesses or injuries, pelvic inflammatory disease or exposure to sexually transmitted diseases, and unusual childhood disorders, 6) previous abnormal pap smears and any subsequent treatment, 7) current medications and allergies, 8) occupation and use of tobacco, alcohol, and other drugs, 9) family history of birth defects, mental retardation, or reproductive failure, and 10) symptoms of thyroid disease, pelvic or abdominal pain, galactorrhea, hirsutism, and dyspareunia.

# Physical Examination:

- \* Physical examination should note the patient's weight and body mass index and identify any 1) thyroid enlargement, nodule, or tenderness, 2) breast secretions and their character, 3) signs of androgen excess, 4) pelvic or abdominal tenderness, organ enlargement, or mass, 5) vaginal or cervical abnormality, secretions, or discharge, 6) uterine size, shape, position, and mobility, 7) adnexal mass or tenderness, and 8) cul-de-sac mass, tenderness, or nodularity

# Diagnostic Evaluation:

## 2. Ovulatory Factors:

- \* Menstrual history
- \* BBT?
- \* Serum progesterone
  - \*  $>3.0$  ng/ml = ovulation
  - \*  $>10$  ng/ml correlates with “in phase” histology (we time 8 days post LH surge)
- \* LH kits
- \* Endometrial biopsy ?- (controversies persist)
- \* Serial transvaginal ultrasound ( we spot check based on day of cycle & (+) LH kit)
- \* TSH,PRL,FSH ( with E2!)

# Endocrine Society Guidelines:

- \* “Benefits of universal screening for thyroid dysfunction may not be justified by the current evidence.”
- \* Targeted case findings **is** recommended however for:
  - \* Women with infertility
  - \* Women with a history of spontaneous AB or preterm delivery.


(JCEM, 2007)

WHY?

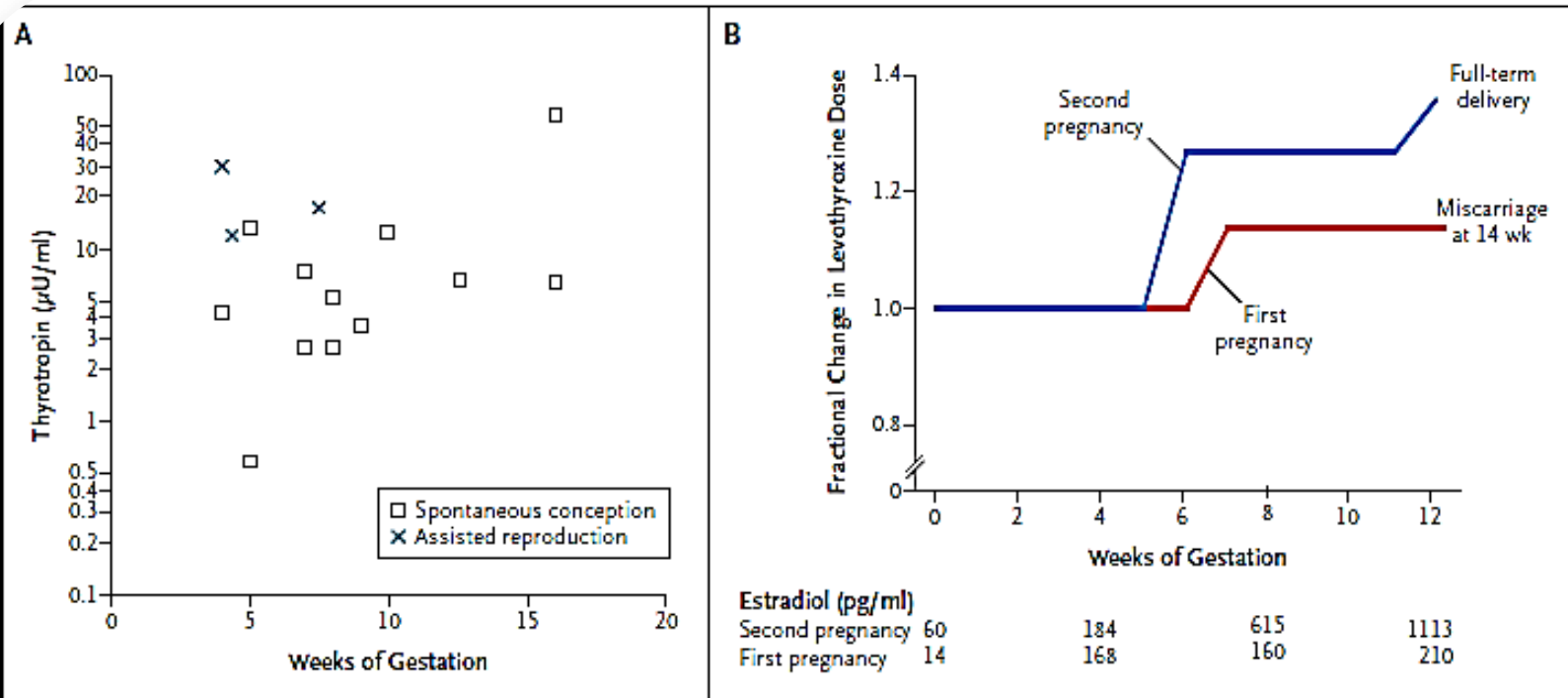
# Thyrotoxicosis

- \* ↑ Sex hormone binding globulin (SHBG) leading to:
  - \* Increased E<sub>2</sub>, E<sub>1</sub>, T, dihydrotestosterone
  - \* Increased androgen to estrogen conversion
- \* Baseline gonadotropin levels increased, midcycle peaks reduced or absent

# Hypothyroidism

- \*  Sex hormone binding globulin (SHBG) leading to :
  - \* Decreased E<sub>2</sub>, T.
- \* Decreased androgen secretion.
- \* Normal baseline gonadotropin levels but midcycle peaks blunted or absent.

# Effect of Increased E2:



**Figure 3. Evidence Implicating Changes in Estradiol as a Key Contributor to Increased Levothyroxine Requirements during Early Pregnancy.**

Panel A shows thyrotropin concentrations (on a logarithmic scale) in early pregnancy at the time of the first levothyroxine adjustment. Panel B shows changes in Subject 5 in the levothyroxine dose and in serum estradiol concentrations during her two pregnancies. To convert the values for estradiol to picomoles per liter, multiply by 3.67.

Overt and subclinical  
hypothyroidism have adverse  
effects on the course of  
pregnancy and development of  
the fetus.

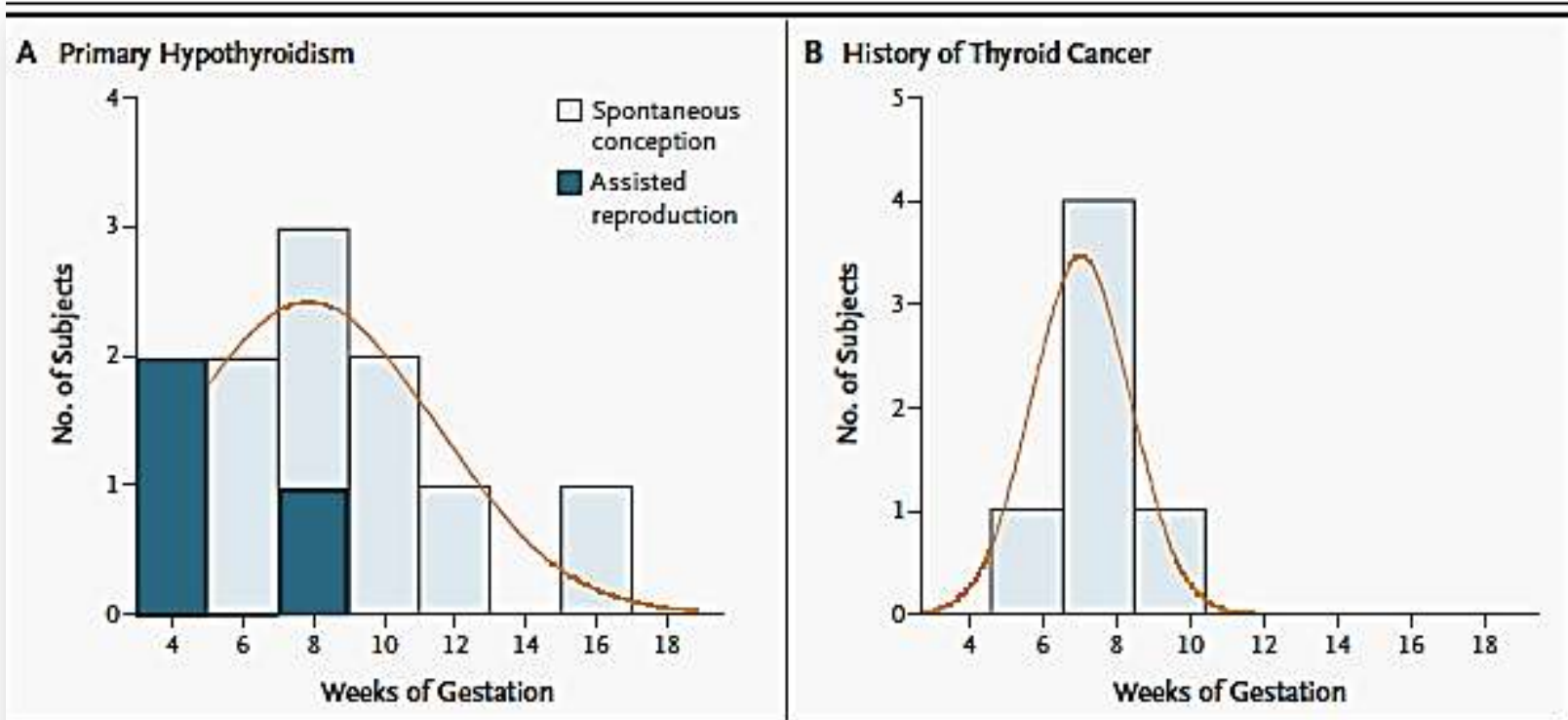
# Hypothyroidism

- \* Impaired fetal intellectual development.
- \* Increased rate of fetal death.
- \* Positive association between positive thyroid antibodies and pregnancy loss ( increased maternal age ??).
- \* One adequately designed interventional study has demonstrated decreased spontaneous AB rate in thyroid antibody (+), euthyroid women .

(Negro, JCEM, et al 2006)

Therefore TSH every 4-5 weeks  
in thyroid antibody positive  
patients

# Gestational Week of Initial Increase of Levothyroxine Dose



**Figure 2. Gestational Week of the Initial Increase in the Levothyroxine Dose.**

Panel A shows the week at which the levothyroxine dose was first increased in 11 women with primary hypothyroidism; in these women, the dose was increased when the thyrotropin concentration was greater than 5.0  $\mu\text{U}$  per milliliter. Panel B shows the week at which the levothyroxine dose was first increased in women with a history of thyroid cancer; in these women, the dose was increased when the thyrotropin concentration was greater than 0.5  $\mu\text{U}$  per milliliter.

# Hypothyroidism

- \* If hypothyroidism diagnosed prior to pregnancy, adjust preconception thyroxine dose to TSH level  $\leq 2.5 \mu\text{U/ml}$  prior to pregnancy. (JCEM 2007)
- \* Once pregnant, (unless recently placed on thyroxine or adjusted) double dose of thyroxine 2x/week (=29% increase in dose) TSH levels q4-5 weeks.

(Alexander et al ,NEJM, 2004)

# 3. Cervical Factors:

- \* Routine PCT unnecessary- “Reserve for patients whom results will clearly influence treatment strategy.”

# 4. Uterine Factors:

- \* HSG
- \* Ultrasound
- \* Hysteroscopy

“Examination of the uterine cavity is an integral part of any thorough evaluation... the method chosen... should be tailored to the needs of the individual patient.”

# Submucous Myomas

- \* Detrimental to fertility, increased SAB rate.
- \* Hysteroscopic resection improves fertility (except perhaps for type 2 submucous fibroids).

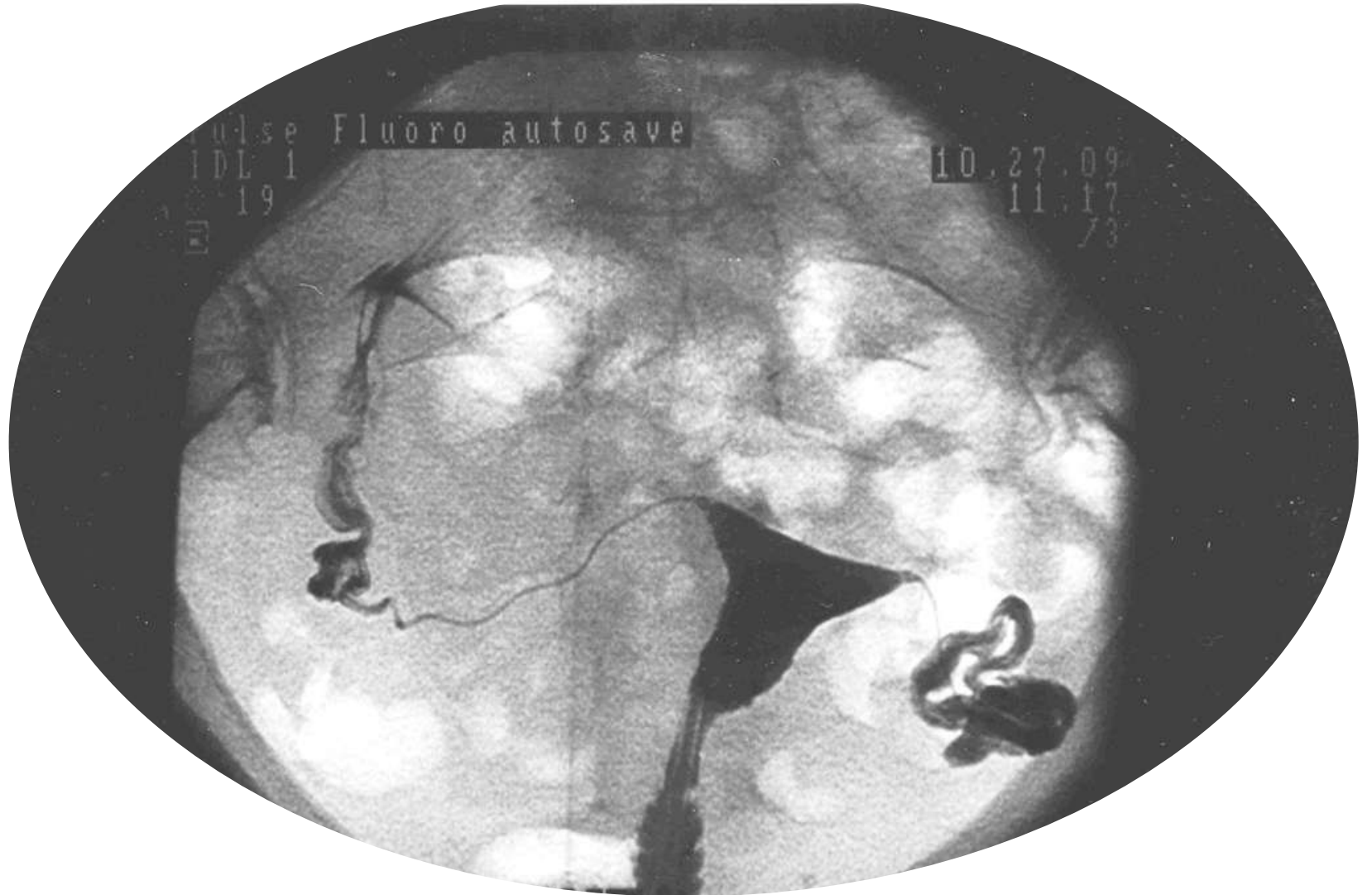
(Shekeir et al, F&S, 2009)

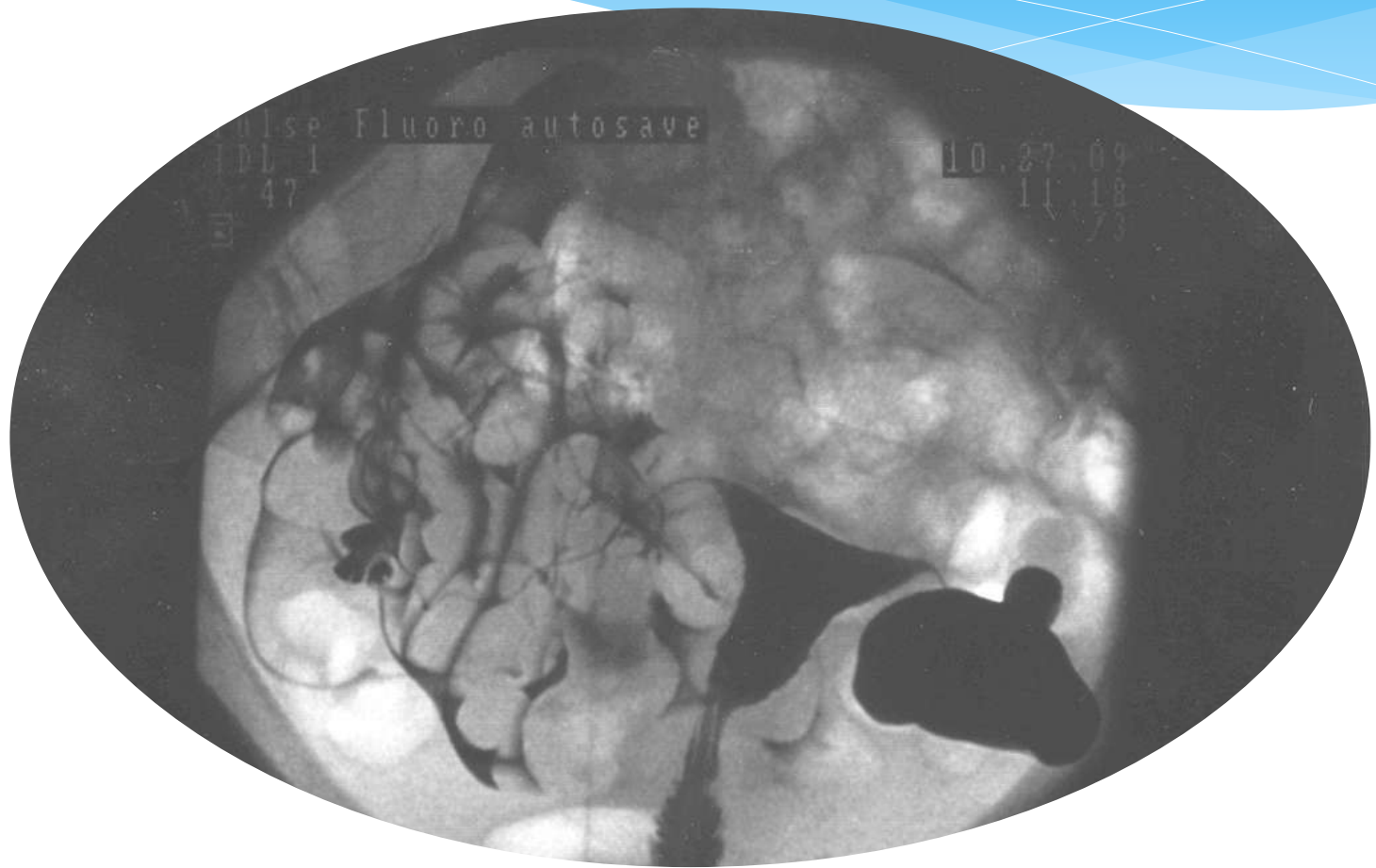
# 5. Tubal Factors:

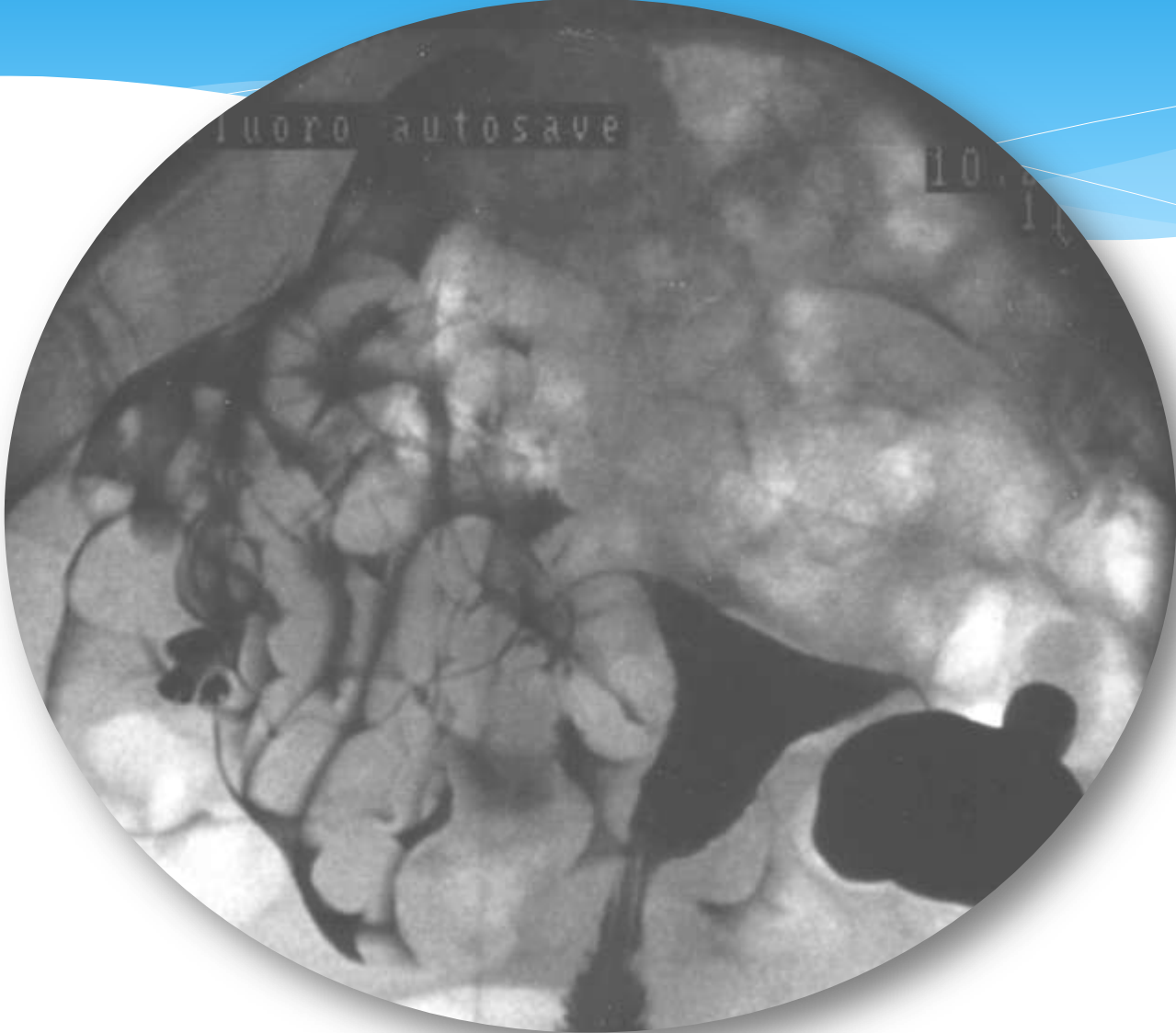
- \* HSG (can demonstrate proximal SIN)
- \* Laparoscopy
- \* Selective Tubal cannulation (we reserve for highly select cases).

“All available methods... have technical limitations... further evaluation with a second, complementary method is prudent whenever diagnosis or best strategy is uncertain.”









# 6. Endometriosis or other pelvic Pathology:

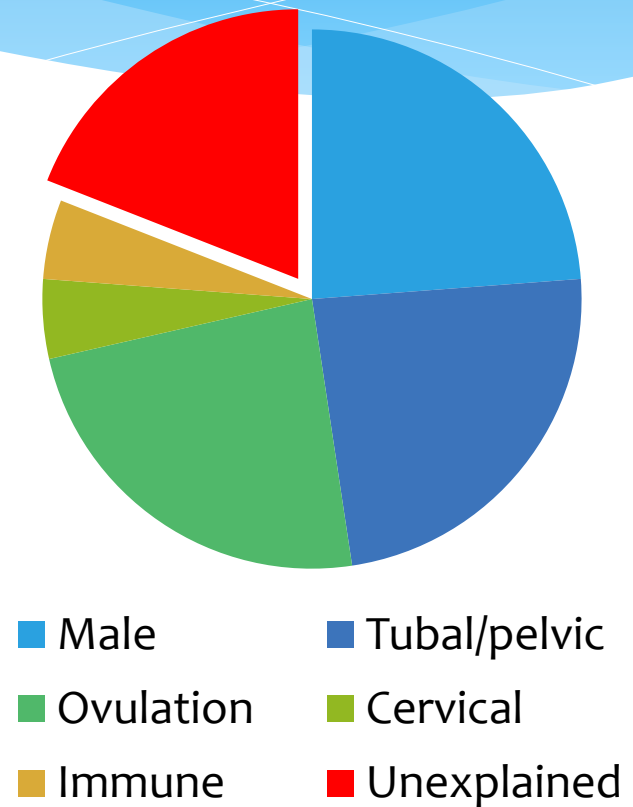
- \* Ultrasound (endometriomas)
- \* Laparoscopy

# 7. Ovarian Reserve:

“Evaluation of ovarian reserve should be performed in selected patients to obtain prognostic information that may have significant influence on treatment recommendations.”

# “Unexplained Infertility” – no Longer a Common Diagnosis

- \* **Male factors (50%)**
  - \* Primary or sole (25%)
  - \* Contributory (25%)
- \* **Female factors**
  - \* anatomical / pelvic / tubal factors (25%)
  - \* hormonal / ovulatory factors (25%)
  - \* cervical factors (5%)
- \* **Immunologic factors (5%)**
- \* **“Unexplained infertility” (15-20%)**

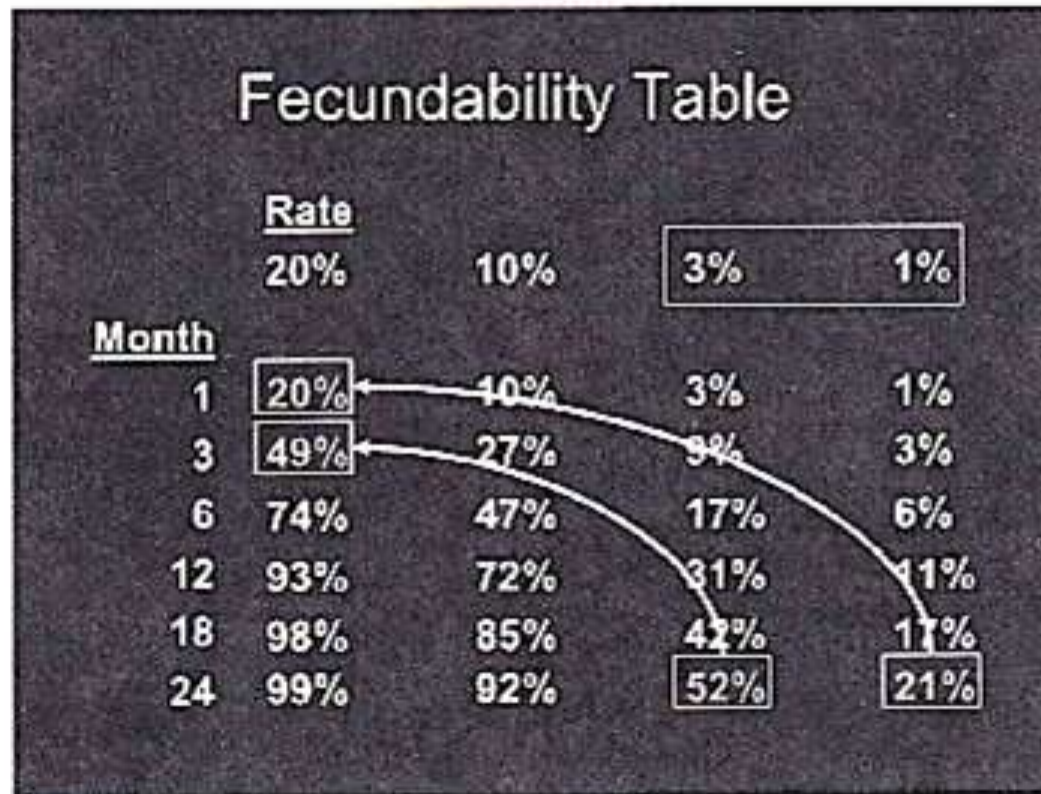


# Testing for Ovarian Reserve:

- \* Better screening tests lead to earlier detection and better prognosis for pregnancy
- \* More aggressive treatment may be started earlier based on results of screening

# Testing for Ovarian Reserve

Cumulative percentage of population pregnant over time as a function of conception rate.



# Ovarian Reserve Tests:

- \* Baseline FSH,LH, E2
- \* CCT
- \* Ovarian volumes and antral follicle counts
- \* AMH

# None of the Tests are Perfect:

- \* There is no value that will absolutely predict pregnancy or not.
- \* Tests should be used for counseling, not for denial of treatment.

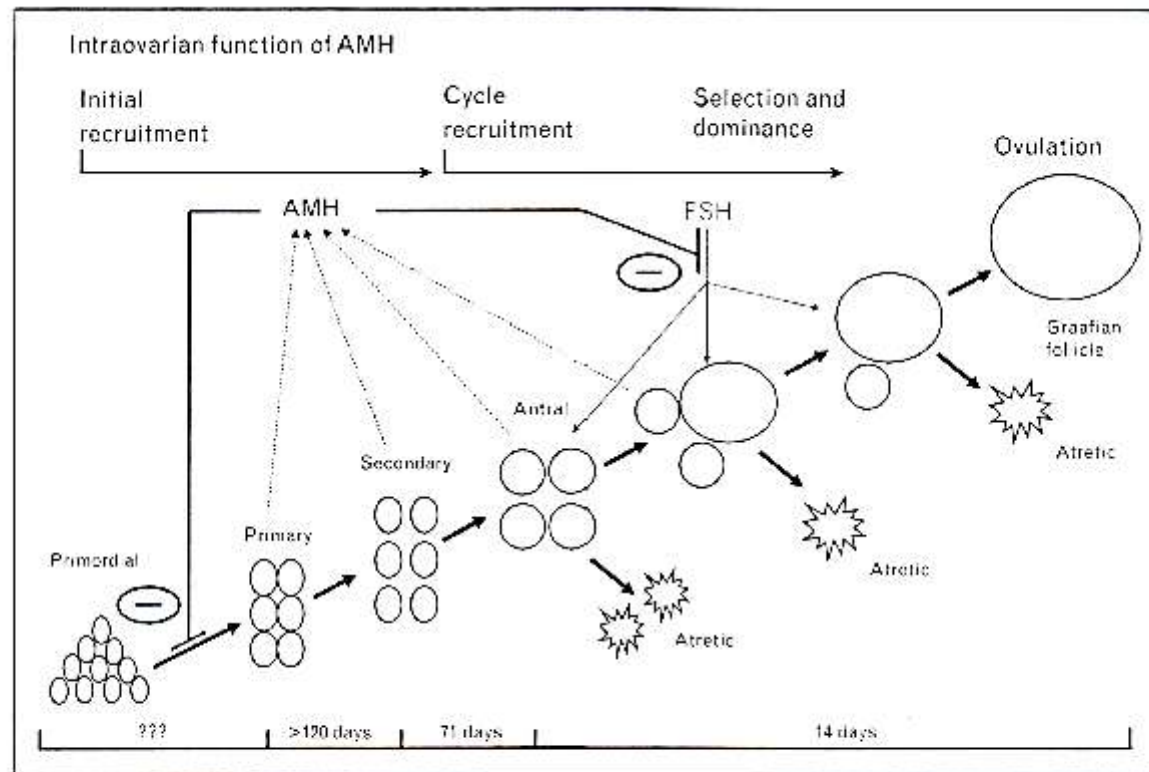
# Ovarian Reserve Testing

- \* CCT & Exogenous FSH ovarian reserve tests have better predictive value for the prediction of pregnancy.
- \* CCT  $>18$  IU/L = 100% specificity but sensitivity of only 25 %.


(Kwee et al F&S, 2008)


# AMH as an Early Warning System

# AMH



First, AMH has an inhibitory role in the initial recruitment and thereby aids in regulating the number of follicles remaining in the primordial pool. Second, AMH has an inhibitory effect on follicular sensitivity to FSH and could therefore play a role in the process of dominant follicle selection. AMH, anti-Müllerian hormone; FSH, follicle-stimulating hormone.


- 
- \* Can measure AMH throughout cycle
  - \* Stable between cycles
  - \* No observer bias



\* AMH has been shown to be the marker best reflecting the gradual decline in reproductive capacity with increasing age. (Van Rooij et al, F&S, 2005)

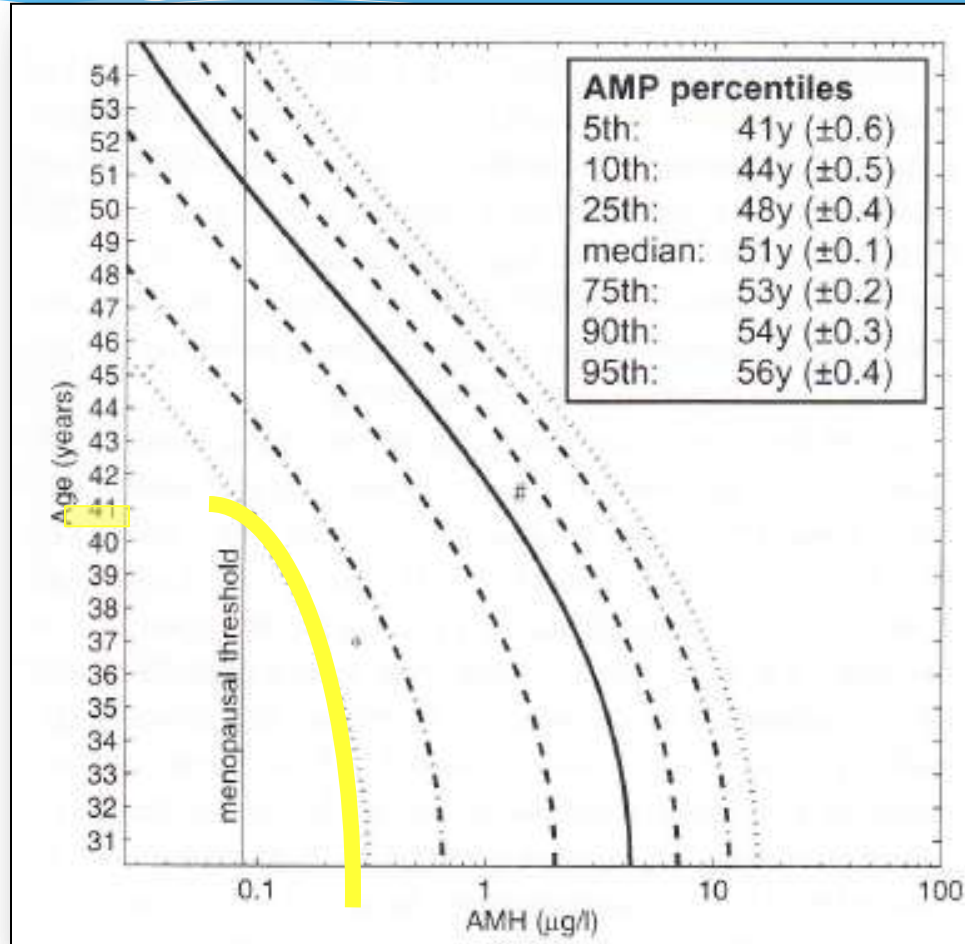
\* AMH falls before changes in other markers such as FSH, inhibin B become apparent.

(Van Rooij et al; Menopause, 2004)

- 
- \* Menopause status >6 years with AMH >0.39 ng/ml
  - \* Reflects a women's reproductive age more realistically than chronologic age alone

(Tehrani et al, Menopause 2009)

# Relationship Between AMH and Age at Menopause



# The New Perinatal Screening Paradigm...

\* Or pickle, or Pandora's box ??...



\* “One should proceed with genetic testing in much the same way as in picking one’s nose:

You need to know what to do with the results before you start”—famous Geneticist

# Screening


- \* NIH Director Francis Collins recently made trenchant remarks about the state of carrier screening in his new book, the Language of Life (Collins,2010): ‘If I were younger and about to start a family, I would want to test myself and encourage my wife to do the same—not just for CF (cystic fibrosis) but for a long list of recessive diseases.... But our current model of delaying carrier screening until a pregnancy is already under way forces couples to make tough choices, and deprives them of pre-conception alternatives that they might have preferred.’

# Screening

- \* Single gene disorders account for at least:
  - \* 10% of pediatric admissions
  - \* 20% of infant mortality
- \* >6000 genetic disorders (most affect less than 200,000 Americans each)
- \* Combine to afflict 25-30 million people in U.S. (NIH, 2010)

# Several Options For Positive Preconception Test Results

- \* Proceed to conception without intervention (knowledge of condition may allow ameliorative options from birth).
- \* PGD
- \* Prenatal testing
- \* Donor gametes

- 
- \* CF,SMA already recommended.
  - \* Ethnicity appropriate screening also already recommended:
    - \*  $\alpha$ ,  $\beta$  thalassemia
    - \* Jewish ethnicity panels
    - \* Sickle cell

# But

- \* “Screening for the most common genetic diseases alone will fail to discover most of the carriers (of Mendelian disease) in the general population.”

(Srinivasan et al, RBO,2010 in press)

# Universal Carrier Screening Tests:

- \* Must have low false negative AND low false positive rates.
- \* Must have high mutation detection rate.
- \* Must be low cost– essentially rules out separate tests for each disease.
- \* Should be as accurate and precise as single gene assays.
- \* Recent advances in genomics appear to make all of this possible.

Counsyl

# Performance Statistics for the Universal Genetic Test

**An extraction from:** Balaji S. Srinivasan, Jason Flannick, A. Scott Patterson, Christopher C. Chang, Tuan Pham, Sharon Young, Amit Kaushal, James Lee, Pasquale Patrizio, Eric A. Evans.  
*A Universal Carrier Test for the Long Tail of Mendelian Disease.* Reproductive BioMedicine Online (*in press*).

## Performance Statistics

We exhaustively validated the Universal Genetic Test on a combination of reference gDNA samples [1], synthetic DNA samples [2-4], and clinical DNA samples. In brief, we achieved extremely high sensitivity, specificity, and positive predictive values by combining multiple redundant probes, a triage strategy, and two-stage follow-up testing for positive carrier couples. Probes in the assay which passed triage had essentially digital accuracy, with either complete success or else no-call on hundreds of control samples per variant. The overall performance results are summarized in Table 1.

Metric	Value	95% Conf. Interval
Accuracy	0.99998	0.999888 – 0.999999
Precision	0.99997	0.99993 – 0.99999
Sensitivity	0.99998	0.99988 – 0.999999
Specificity	> 0.996	0.99643 – 1.0
False Positive Rate	< 0.004	0 – 0.00357
False Negative Rate	0.00002	0.000001 – 0.00012
Positive Predictive Value	> 0.995	0.995 – 1.0
Negative Predictive Value	0.99907	0.99474 – 0.99995

**Table 1** Performance Metrics for Validating the Universal Genetic Test.

We constructed a large gold standard reference database by combining samples from public sources and sequence verified samples, providing large numbers of labeled positive and negative samples for each variant. When used in conjunction with domain knowledge that gave us a priori information on the number of clusters for each variant, we could establish very robust call boundaries with strong separation between genotypes.

# Counsyl

## Performance Comparison

Accuracy and precision are the most informative estimates of the total aggregate error rate of the assay. Both statistics indicate an overall average error rate of approximately 1 in 50,000. To put this performance in context, this means the Universal Genetic Test is a highly multiplex assay which nevertheless compares very favorably to the reported accuracy and precision of existing single gene assays for cystic fibrosis (Table 2). It is also within the range of the top single gene DNA based tests for Tay-Sachs mutations [5], which had 4 errors (false positives + false negatives) per 100,000 couples.

Test	Accuracy	95% CI	Precision	95% CI
eSensor R Cystic Fibrosis Carrier Detection System	99.97%	[0.99924, 0.99991]	99.9%	n/a *
Tag-It™ Cystic Fibrosis Kit (TM Bioscience Corp)	100%	[0.99869, 1]	> 99.99%	[0.99980, 0.99998]
Cystic Fibrosis Genotyping Assay (Celera)	>99.99%	[0.99977, 1]	100%	[0.99990, 1]
InPlex CF Molecular Test (Third Wave Technology)	99.96%	[0.99782, 0.99998]	99.987%	[0.99984, 0.99990]
Universal Genetic Test (Counsyl)	99.998%	[0.99988, 0.999999]	99.997%	[0.99993, 0.99999]

- \* 105 Mendelian diseases, but recently decreased.
- \* Saliva sample
- \* 35% of samples are carriers of at least one (1) disease.
- \* Carrier couple frequency = 0.6% -0.8%

# Disease List

- \* [ABCC8-Related Hyperinsulinism](#)
- \* [Achondrogenesis Type 1B](#)
- \* [Achromatopsia](#)
- \* [Alkaptonuria](#)
- \* [Alpha-1 Antitrypsin Deficiency](#)
- \* [Andermann Syndrome](#)
- \* [ARSACS](#)
- \* [Aspartylglycosaminuria](#)
- \* [Ataxia With Vitamin E Deficiency](#)
- \* [Ataxia-Telangiectasia](#)
- \* [Autosomal Recessive Polycystic Kidney Disease](#)
- \* [Bardet-Biedl Syndrome, BBS1-Related](#)
- \* [Bardet-Biedl Syndrome, BBS10-Related](#)
- \* [Beta Thalassemia](#)
- \* [Biotinidase Deficiency](#)
- \* [Bloom Syndrome](#)
- \* [Canavan Disease](#)
- \* [Carnitine Palmitoyltransferase IA Deficiency](#)
- \* [Carnitine Palmitoyltransferase II Deficiency](#)
- \* [Cartilage-Hair Hypoplasia](#)
- \* [Choroideremia](#)
- \* [CLN5-Related Neuronal Ceroid Lipofuscinosis](#)
- \* [Congenital Disorder of Glycosylation Type Ia](#)
- \* [Congenital Disorder of Glycosylation Type Ib](#)
- \* [Congenital Finnish Nephrosis](#)
- \* [Cystic Fibrosis](#)
- \* [Cystinosis](#)
- \* [Diastrophic Dysplasia](#)
- \* [Factor V Leiden Thrombophilia](#)
- \* [Factor XI Deficiency](#)
- \* [Familial Dysautonomia](#)
- \* [Familial Mediterranean Fever](#)
- \* [Fanconi Anemia Type C](#)

- \* [Fumarase Deficiency](#)
- \* [Galactosemia](#)
- \* [Gaucher Disease](#)
- \* [GJB2-Related DFNB 1 Nonsyndromic](#)
- \* [Hearing Loss and Deafness](#)
- \* [Glucose-6-Phosphate Dehydrogenase Deficiency](#)
- \* [Glutaric Acidemia Type 1](#)
- \* [Glycogen Storage Disease Type Ia](#)
- \* [Glycogen Storage Disease Type Ib](#)
- \* [Glycogen Storage Disease Type III](#)
- \* [Glycogen Storage Disease Type V](#)
- \* [GRACILE Syndrome Hereditary Fructose Intolerance](#)
- \* [Hereditary Thymine-Uraciluria](#)
- \* [Herlitz Junctional Epidermolysis Bullosa, LAMA3-Related](#)
- \* [Herlitz Junctional Epidermolysis Bullosa, LAMB3-Related](#)
- \* [Herlitz Junctional Epidermolysis Bullosa, LAMC2-Related](#)
- \* [Hexosaminidase A Deficiency](#)
- \* [HFE-Associated Hereditary](#)
- \* [Hemochromatosis](#)
- \* [Homocystinuria Caused by Cystathionine Beta-Synthase Deficiency](#)
- \* [Hurler Syndrome](#)
- \* [Hyperornithinemia-Hyperammonemia](#)
- \* [Homocitrullinuria Syndrome](#)
- \* [Hypophosphatasia, Autosomal Recessive](#)
- \* [Inclusion Body Myopathy 2](#)
- \* [Infantile Refsum Disease](#)
- \* [Isovaleric Acidemia](#)
- \* [Krabbe Disease](#)
- \* [Leigh Syndrome, French-Canadian Type](#)
- \* [Limb-Girdle Muscular Dystrophy Type 2E](#)
- \* [Long Chain 3-Hydroxyacyl-CoA Dehydrogenase Deficiency](#)
- \* [Maple Syrup Urine Disease Type 1B](#)
- \* [Maple Syrup Urine Disease Type 3](#)

- \* [Medium Chain Acyl-CoA Dehydrogenase Deficiency](#)
- \* [Metachromatic Leukodystrophy](#)
- \* [Mucopolidosis IV](#)
- \* [Muscle-Eye-Brain Disease MYH-Associated Polyposis](#)
- \* [Niemann-Pick Disease Type A](#)
- \* [Niemann-Pick Disease Type C](#)
- \* [Nijmegen Breakage Syndrome](#)
- \* [Northern Epilepsy](#)
- \* [Pendred Syndrome](#)
- \* [Phenylalanine Hydroxylase Deficiency](#)
- \* [Polyglandular Autoimmune Syndrome Type 1](#)
- \* [Pompe Disease](#)
- \* [PPT1-Related Neuronal Ceroid Lipofuscinosis](#)
- \* [Primary Hyperoxaluria Type 1](#)
- \* [Primary Hyperoxaluria Type 2](#)
- \* [Pycnodysostosis](#)
- \* [Recessive Multiple Epiphyseal Dyspla](#)
- \* [Rhizomelic Chondrodysplasia Punctata Type 1](#)
- \* [Salla Disease](#)
- \* [Segawa Syndrome](#)
- \* [Short Chain Acyl-CoA Dehydrogenase Deficiency](#)
- \* [Sickle Cell Disease](#)
- \* [Sjogren-Larsson Syndrome](#)
- \* [Smith-Lemli-Opitz Syndrome](#)
- \* [Spinal Muscular Atrophy](#)
- \* [Tay-Sachs Disease](#)
- \* [TPP1-Related Neuronal Ceroid Lipofuscinosis](#)
- \* [Tyrosinemia Type I](#)
- \* [Usher Syndrome Type 1F](#)
- \* [Usher Syndrome Type 3](#)
- \* [Wilson Disease](#)
- \* [X-Linked Juvenile Retinoschisis](#)

# Pathway Genomics

- \* Saliva Based
- \* 76 recessive diseases
- \* Does not screen for SMA (Supposedly to begin at end of quarter one).

Pathway Genomics' extended carrier status genetic testing service currently screens for mutations that cause 76 recessive genetic diseases.

*Note: this list is subject to change. Please contact a Pathway representative for the most current list.*

*Pre-Pregnancy Planning Insight™: List of Conditions Covered*

3-Methylcrotonyl-CoA carboxylase deficiency	Dihydropyrimidine dehydrogenase deficiency	Hemoglobin C	Polycystic kidney disease
Acrodermatitis enteropathica	Dubin-Johnson syndrome	Hemoglobin E	Pompe disease
Alpha-1 antitrypsin deficiency	Ehlers-Danlos syndrome, dermatosparaxis	HMG-CoA lyase deficiency	Prekallikrein deficiency
Amyotrophic lateral sclerosis	Ehlers-Danlos syndrome, hypermobility	Homocystinuria, cblE type	Propionic acidemia
Argininosuccinate lyase deficiency	Ehlers-Danlos syndrome, kyphoscoliotic	Homocystinuria, classic	Prothrombin deficiency
Autoimmune polyglandular syndrome, type I	Ethylmalonic aciduria	Hurler syndrome	Rh-null syndrome
Bartter syndrome type 4A	Factor XI deficiency	Krabbe disease	Rickets, pseudovitamin D-deficiency
Beta-ketothiolase deficiency	Familial dysautonomia	Lipoprotein lipase deficiency, familial	Sandhoff disease
Beta-thalassemia	Familial Mediterranean fever	Maple syrup urine disease	Short-chain acyl-CoA dehydrogenase deficiency
Biotinidase deficiency	Fanconi anemia	Medium-chain acyl-CoA dehydrogenase deficiency	Sick sinus syndrome
Bloom syndrome	Galactokinase deficiency	Methylmalonic acidemia	Sickle cell disease
Canavan disease	Galactosemia	MTHFR deficiency	Spherocytosis, hereditary
Carnitine deficiency, primary systemic	Gaucher disease	Mucopolipidosis II	Tay-Sachs disease
Cerebrotendinous xanthomatosis	Glutaric acidemia, type 1	Mucopolipidosis III	Tay-Sachs pseudodeficiency
Citrullinemia type I	Glycogen storage disease, type 1A	Mucopolipidosis IV	Thrombocytopenia, congenital amegakaryocytic
Corticosterone methyl oxidase deficiency	GM1-gangliosidosis	Multiple carboxylase deficiency	Tyrosinemia
Crigler-Najjar syndrome	Hearing loss, DFNB1 and DFNB9 nonsyndromic	Nephrotic syndrome, steroid-resistant	Very long-chain acyl-CoA dehydrogenase deficiency
Cystic fibrosis	Hearing loss, DFNB59 nonsyndromic	Niemann-Pick disease	Von Willebrand disease type 2 Normandy
Diabetes, permanent neonatal	Hemochromatosis	Phenylketonuria	Von Willebrand disease type 3

# Ambry Genetics

- \* Blood sample
- \* 78 recessive disorders
- \* Does not screen for SMA

# AmbrySCREEN

The following is a list of the disease conditions, along with the genes, that are included in this panel. Some genes can cause multiple conditions and these have been grouped together in those instances.

- 3-Hydroxy-3-methylglutaric aciduria, HMG- CoA lyase deficiency HMGCL
- Achondrogenesis type 1B SLC26A2
- Andermann Syndrome (Agenesis of the Corpus Colosum with Peripheral Neuropathy) SLC12A6
- Argininosuccinate aciduria ASL
- Aspartylglucosaminuria AGA
- Ataxia Telangiectasia ATM
- Atelosteogenesis type 2 SLC26A2
- Bardet-Biedl syndrome 1 BBS1
- Bardet-Biedl syndrome 10 BBS10
- Batten Disease, Juvenile Neuronal Ceroid Lipofuscinosis CLN3
- Beta ketothiolase deficiency ACAT1
- Biotinidase Deficiency; Multiple Carboxylase Deficiency BTB
- Bloom Syndrome BLM
- Carnitine-acylcarnitine Translocase Deficiency (CACT) SLC25A20
- Carnitin Palmitoyltransferase II Deficiency CPT2
- Carnitine Uptake Defect SLC22A5
- Canavan ASPA
- Carbamoylphosphate synthetase (CPS) CPS1
- Cartilage-Hair Hypoplasia RMRP
- Ceroid Lipofuscinosis, Neuronal 2; CLN2 TPP1
- Ceroid Lipofuscinosis, Neuronal 1; CLN1 PPT1
- Citrullinemia type I ASS1
- Creatine transporter defect, X-linked MR with seizures, short stature, and midface hypoplasia SLC6A8
- Cystic Fibrosis CFTR
- Diastrophic Dysplasia SLC26A2
- Dihydropyrimidine Dehydrogenase Deficiency DPYD
- Ethylmalonic Encephalopathy ETHE1
- Familial Dysautonomia IKBKAP
- Familial Mediterranean Fever MEFV
- Fanconi Type C FANCC
- Galactokinase Deficiency, Galactosemia II, GALK deficiency GALK1
- Galactosemia GALT
- Glutaric Acidemia type 1 (GA-1) GCDH
- Glutathione Synthetase Deficiency GSS
- Glycogen Storage Disease type 1a G6PC
- Glycogen Storage Disease type 1b SLC37A4
- GRACILE syndrome BCS1L
- Guanidinoacetate Methyltransferase Deficiency GAMT
- Hereditary Fructose Intolerance, Fructosemia ALDOB
- Holocarboxylase Synthetase Deficiency HLCS
- Homocystinuria CBS
- Hurler, Scheie, Hurler-Scheie disease (MPS1) IDUA
- Hyperoxaluria type 1 AGXT
- Hyperoxaluria type 2 GRHPR
- Hyperornithinemia-Hyperammonemia- Homocitrullinuria Syndrome (HHH) • SLC25A15
- Hypophosphatasia, AR ALPL
- Krabbe disease, GALC Deficiency GALC
- Leigh Syndrome, French-Canadian Type LRPPRC
- Long-chain L-3- hydroxyacyl-CoA dehydrogenase (LCHAD) HADHA
- Maple Syrup Urine Disease BCKDHA
- Medium-chain acyl-coenzyme A dehydrogenase (MCAD) ACAD
- Methylmelonic Aciduria and Homocystinuria, cblc Type MMACH
- Methylmalonic Aciduria - MUT related MUT
- Methylmalonic Aciduria (cobalamin deficiency) cblA type MMAA
- Methylmalonic Aciduria (cobalamin deficiency) cblB type MMAB
- Mucopolidosis type IV MCOLN1
- Nephrosis 1, congenital, Finnish type NPHS1
- Nieman Pick Type A SMPD1
- Nieman Pick Type B SMPD1
- Nonketotic hyperglycinemia (NKH); Glycine Decarboxylase GLDC
- Ornithine Transcarbamylase Deficiency OTC
- Phenylketonuria (PKU) PAH
- Polycystic kidney and hepatic disease; Congenital Hepatic Fibrosis; Caroli Disease PKHD1
- Pompe disease (Glycogen storage disease type II) GAA
- Progressive Epilepsy with Mental Retardation (EPMR) CLN8
- Recessive multiple epiphyseal dysplasia SLC26A2
- Rhizomelic Chondrodysplasia Punctata Type 1 PEX7
- Salla Disease SLC17A5
- Severe Combined Immunodeficiency (AR), Adenosine deaminase deficiency ADA
- Sjogren-Larsson syndrome FALDH
- Smith-Lemli-Opitz Syndrome DHCR7
- Steroid-Resistant Nephrotic Syndrome NPHS2
- Tay-Sachs Disease HEXA
- Tyrosinemia Type 1 FAH
- Variant late infantile Neuronal Ceroid Lipofuscinosis CLN5
- Very long-chain acyl-CoA dehydrogenase (VLCAD) ACADVL
- X-linked Severe Combined Immunodeficiency IL2RG
- Zellweger, Neonatal Adrenoleukodystrophy, Infantile Refsum disease PEX1

# Advantages and Limitations:

- \* Screening decisions no longer based on imprecise ethnic categories
- \* Can be offered to all couples preconception, rather than those with a known family history or prenatally
- \* **Risk reducing rather than risk eliminating**

# Advantages and Limitations:

- \* Disease caused by repeat expansions (fragile x), sporadic duplications/deletions (Duchenne muscular dystrophy) and mutations detectable by biochemical techniques are resistant to genotyping-based analysis.
- \* **More than 90% of Mendelian disease burden remains to be accounted for.**
- \* Real future is diagnostic resequencing; whole genome or targeted regions.

No legal cases reported by  
Physicians Insurance on  
failure to conduct genetic  
screening.

# Nationally :

- \* “Wrongful life” claims mostly not recognized (recovery at majority).
  - \* Damages allowed however in Washington, New Jersey and California.
- \* “Wrongful birth” claims absolutely recognized (recovery at minority for parents).
  - \* *Siemieniec v Lutheran General Hospital*

# Molloy v Meier

- \* Minnesota, 2004
- \* Statute that prohibited wrongful birth action did not preclude malpractice action against doctors in which mother alleged that conception, rather than abortion, would have been avoided had doctors correctly diagnosed mothers transferable genetic disorder.

# Conclusions:

- \* Ultrasound has become increasingly useful in an infertility evaluation.
- \* All infertility and SAB patients should be screened for hypothyroidism.
- \* Consider ovarian reserve screening sooner.
- \* Each ovarian reserve test has both strengths and weaknesses, but as a group may allow more informed counseling of the infertile couple.
- \* Extended preconception screening is here and will become increasingly robust.



OVERLAKE REPRODUCTIVE HEALTH

*Setting the Standard*

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