Comparing the Likely Outcomes of Different Pregnancy Testing Protocols: Can a Model Help?

Evan R. Myers, MD, MPH

CLINICAL TRIALS TRANSFORMATION INITIATIVE

What are “Models”?

- Not statistical model, although statistics are important
- Methods to synthesize evidence and estimate likely outcomes of different decisions
  - Can include evidence from a variety of sources
  - Can illustrate impact of uncertainty about evidence on the likely outcomes
    - Can do “What If” scenarios, even for variables for which there’s no data

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Advantages of Models

- Can compare a large number of possible choices/scenarios
- Can include scenarios that would difficult or unethical to investigate (e.g., cervical cancer screening intervals)
- Can identify most important factors affecting the decision
  - Prioritize research

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Disadvantages

- Dependent on assumptions, evidence
  - "Garbage in, garbage out"
  - Some things are "unknowable unknowns"
- Trade-off between how closely model approximates "real world" and model complexity (time to build and analyze model)
- Can be difficult to explain analysis and results
  - "Black box"

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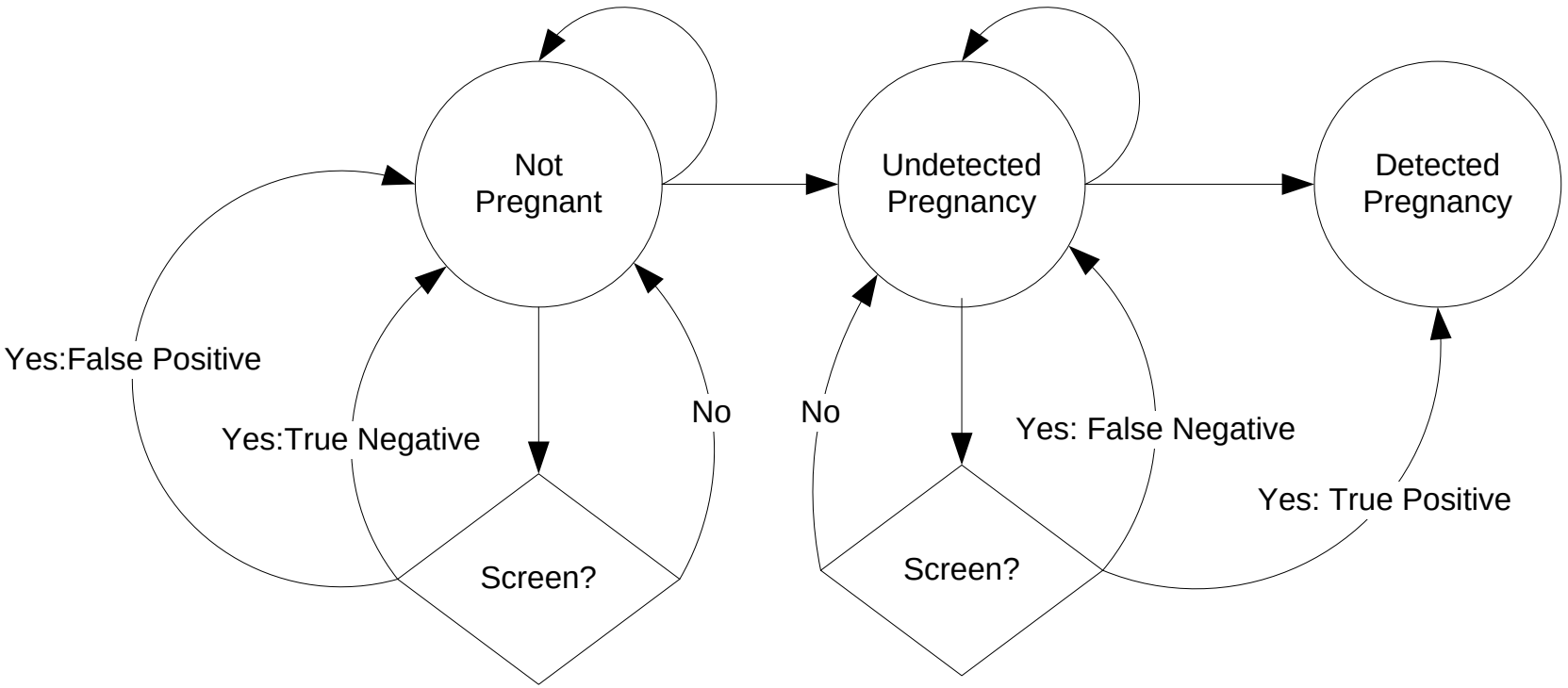
Modeling Pregnancy Testing



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Modeling Pregnancy Testing

- Stochastic
  - Values for probabilities drawn from distributions
- Microsimulation
  - Simulate a cohort of “subjects” who differ on important characteristics that determine outcome
  - Each “subject” is run through the model, results recorded, and averaged together

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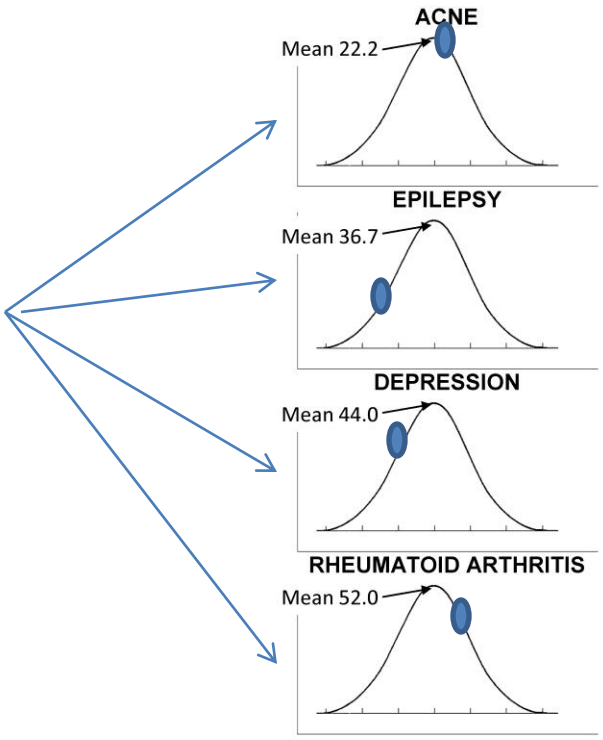
AGE DISTRIBUTIONS



"Subject 1"

Age: 23

Age: 25

Age: 40

Age: 54

Age≥55

Not of childbearing potential

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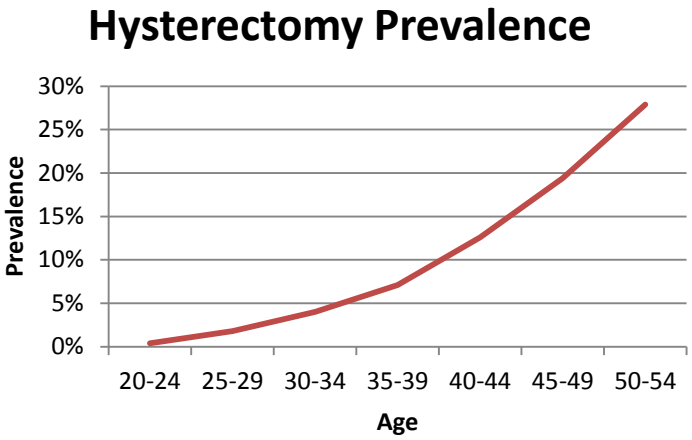
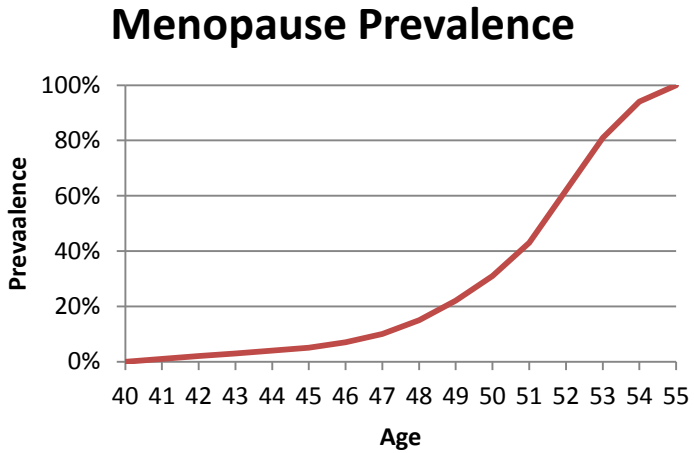
Age



Hysterectomy

Not of childbearing potential

No Hysterectomy



Menopause

No Menopause

Continue

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Age →

Method	Age					
	15-19	20-24	25-29	30-34	35-39	40-44
Female sterilization	0.0%	2.5%	16.2%	31.4%	40.1%	52.3%
Male sterilization	0.0%	0.8%	3.6%	8.9%	17.6%	20.5%
OCP	60.7%	57.3%	41.6%	29.1%	21.4%	11.9%
LARC	5.6%	7.7%	9.0%	8.5%	6.7%	4.3%
Injectable hormones	9.7%	5.4%	5.6%	2.4%	1.0%	1.2%
Barrier methods	24.0%	26.3%	24.0%	19.6%	13.2%	9.8%

→ Contraceptive method "assigned"

Assumed
- Subjects already on method for at least 12 months
- Subjects would not change methods for study

- Model can easily be adjusted to constrain contraceptive methods
- Model can output method-specific outcomes

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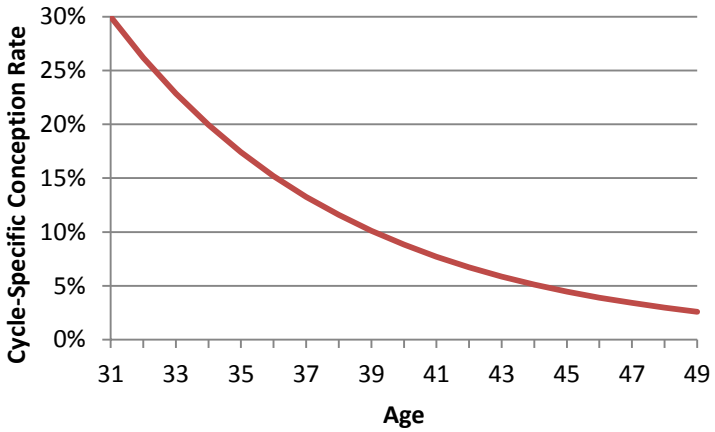
Pregnancy probability/cycle = 30%

Age≤30

Age

Age>30



"Pregnancy" = Conception resulting in detectable hCG in serum and/or urine

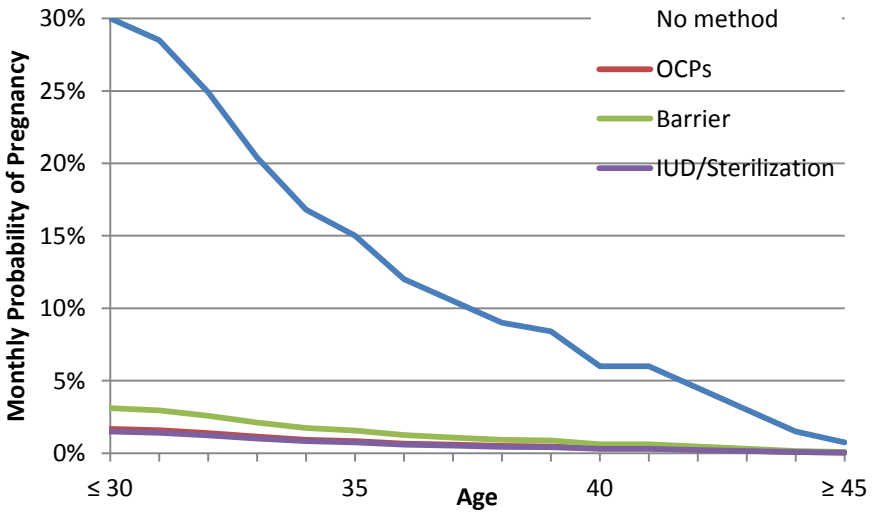
Possible outcomes:

- Live birth:
- Clinical miscarriage
- "Occult" loss (around time of expected menses)

CLINICAL TRIALS TRANSFORMATION INITIATIVE

Contraceptive method

Method	12 Month Failure Rate	Per Cycle Hazard	Hazard Ratio
None	85.00%	13.50%	1.0000
Oral contraceptives	9.00%	0.70%	0.0519
Injectables	6.00%	0.45%	0.0333
Barrier methods	18.00%	1.40%	0.1037
CuT IUD	0.80%	0.07%	0.0048
Progestin IUD	0.20%	0.02%	0.0011
Female sterilization	0.55%	0.05%	0.0033
Male sterilization	0.01%	0.01%	0.0008
Hormonal Implant	0.05%	0.00%	0.0003
Hormonal ring/patch	9.00%	0.70%	0.0519



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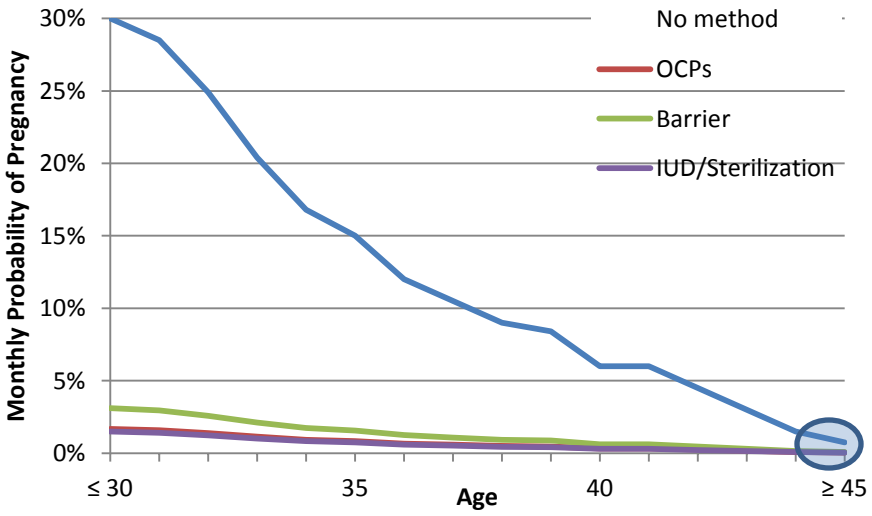

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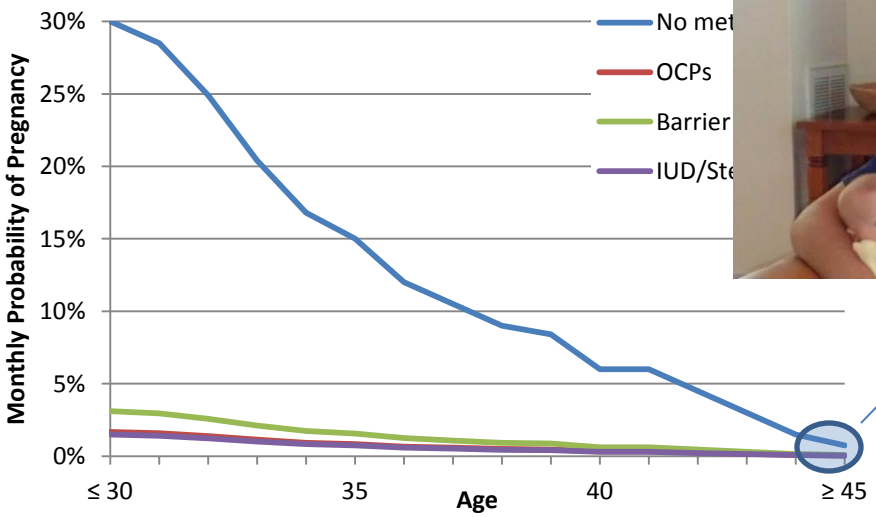

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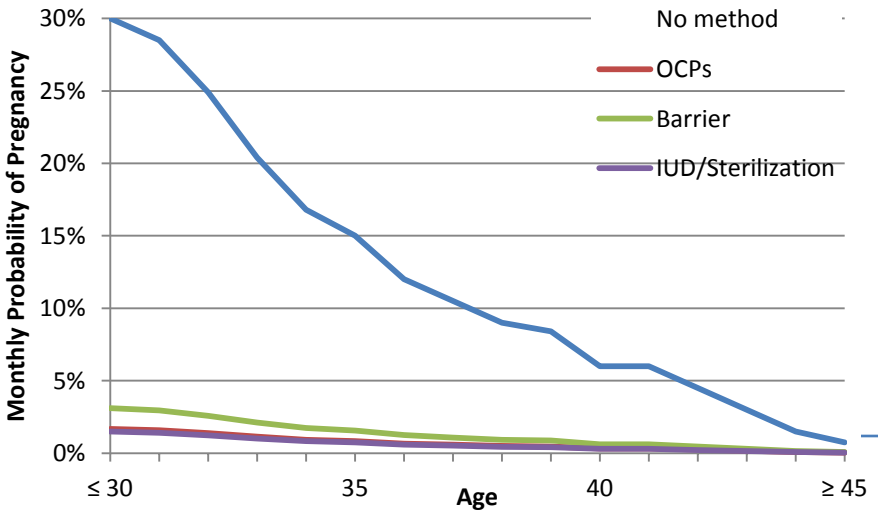

If pregnant

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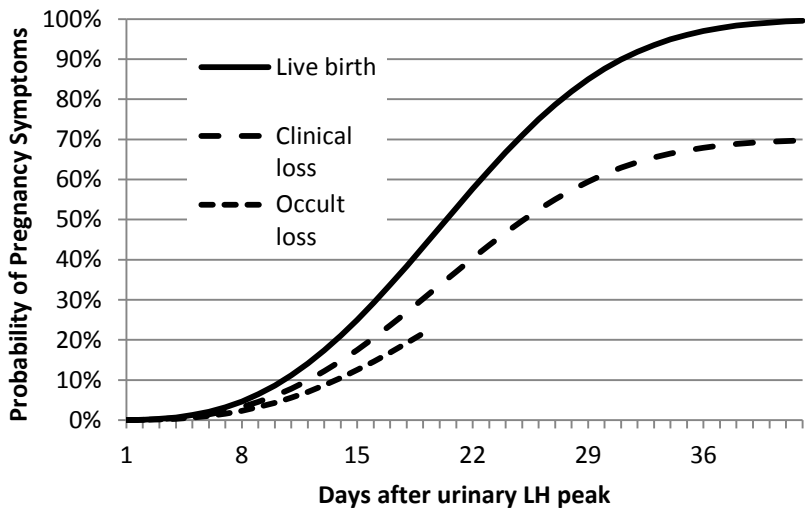
Pregnant

Outcome	Proportion (95% CI)
Live birth	66.0% (58.0-72.9%)
Clinical miscarriage	20.2% (14.4-26.2%)
Occult loss	13.4% (9.3-19.6%)

Not adjusted for age in current version



Time pregnancy detected if no testing

Distribution of gestational age in days at time of random testing

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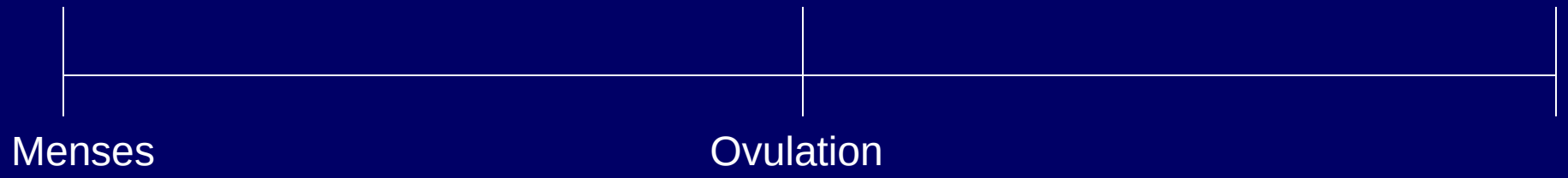
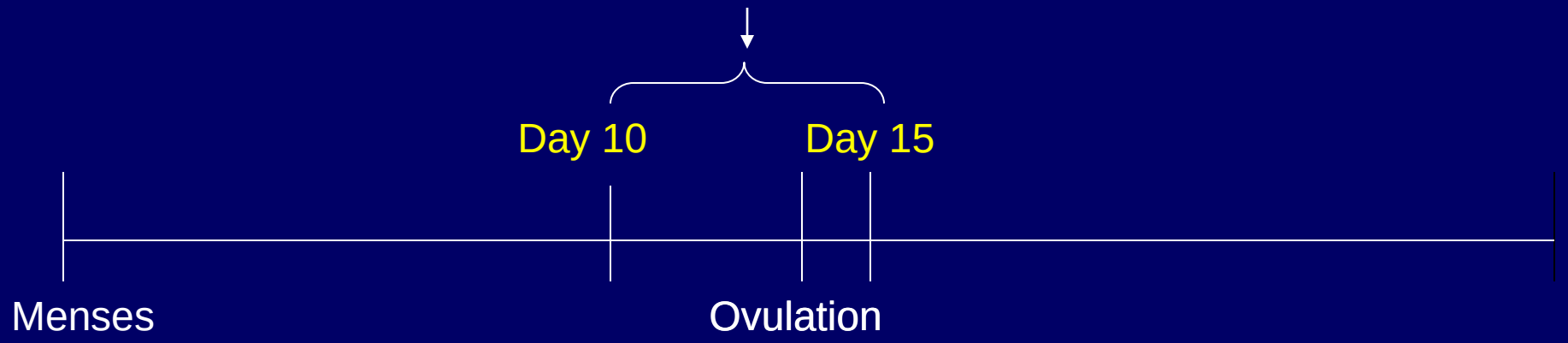
Timing of Conception



CLINICAL TRIALS TRANSFORMATION INITIATIVE

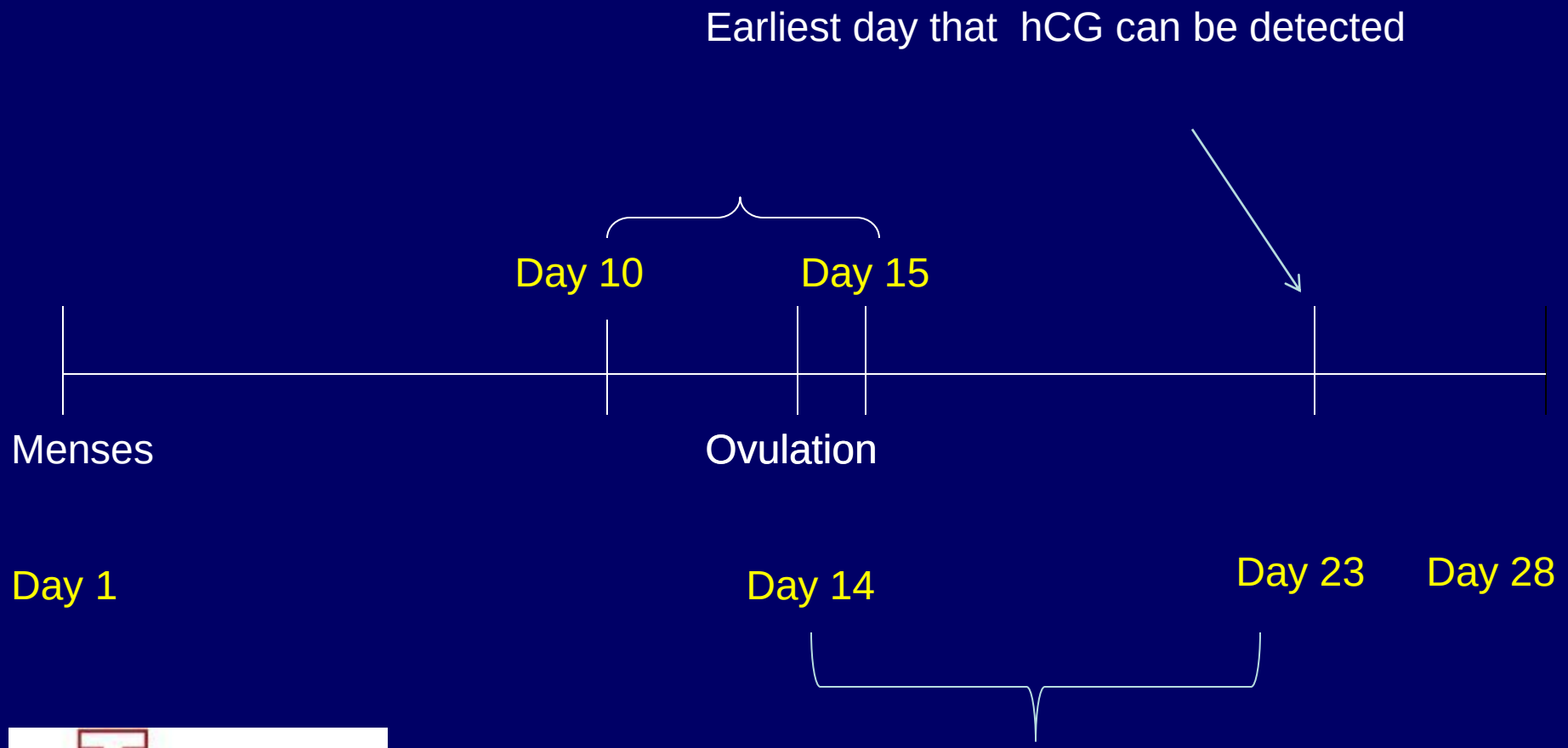
Timing of Conception

Conception can only occur with intercourse during this 6 day window



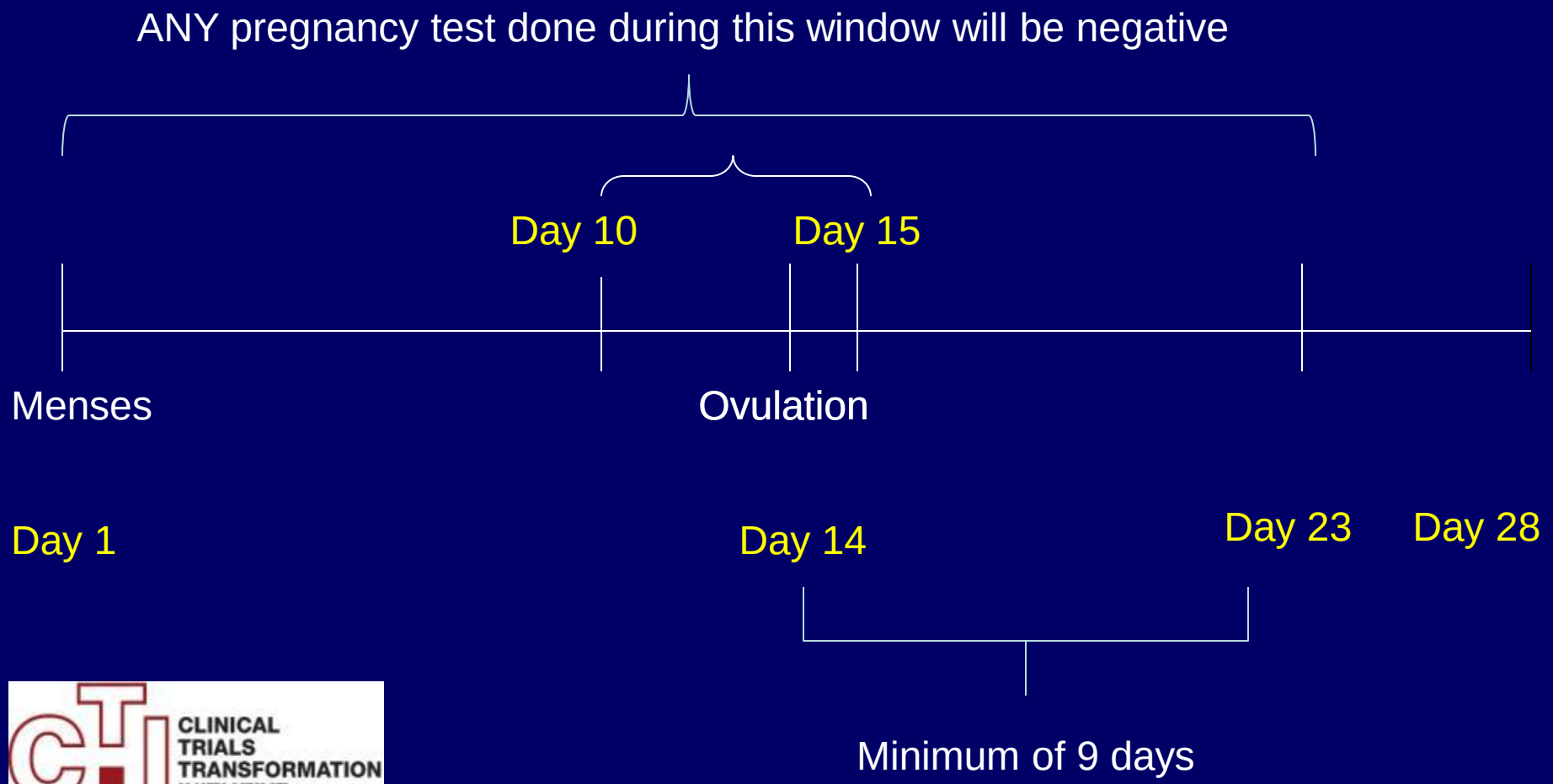
CLINICAL TRIALS TRANSFORMATION INITIATIVE

Timing of Conception



CLINICAL TRIALS TRANSFORMATION INITIATIVE

Timing of Conception



CLINICAL TRIALS TRANSFORMATION INITIATIVE

At start of simulation, "subject" assigned age→

•reproductive potential

•contraceptive method

• probability of having unsuspected pregnancy

Not pregnant

Pregnant

Menstrual cycle day randomly assigned with equal probability

Days post-conception assigned based on probability of symptoms

Cycle length, timing of ovulation randomly assigned
Varies from cycle-to-cycle within subjects

PARAMETER	MEAN (95% CI)
Cycle length (days)	27.7 (23-32)
Within-individual cycle-to-cycle variation (days)	2.8 (0.8-6.2)
Length of luteal phase (days from serum LH peak)*	14.2 (10-18)
Within-individual cycle-to-cycle variation (days)	2.6 (0.3-9)

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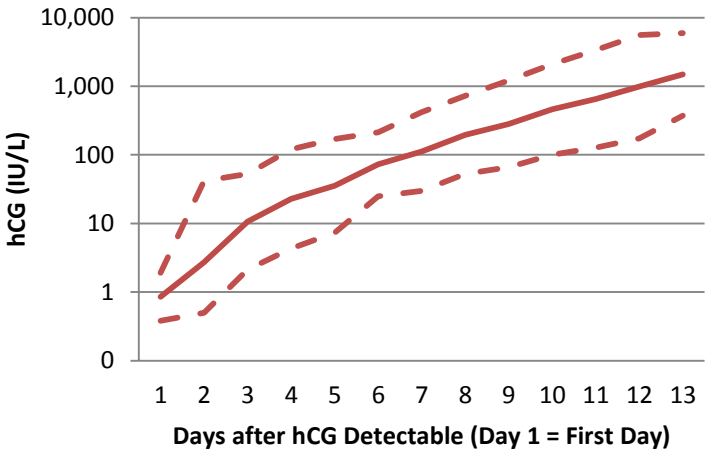
Serum and urine hCG levels "assigned" based on age and cycle day (nonpregnant) or days post-conception (pregnant)

Not pregnant

Source	Mean (95% CI)	Maximum
≤ 40 years old		
Urine		
LH surge ± 3 days	0.32 (0.05,1.6)	9.3
Other days	0.34 (0.11,0.81)	4.0
Serum	1.67 (1.06,2.5)	4.6
41-55 years old		
Urine	0.44 (0.02,2.4)	3.6*
Serum	3.6 (2.6,4.8)	7.7

*99th percentile; reported maximum in paper < reported 99th percentile



Thresholds for pregnancy test sensitivity

- 5 IU/L
- 20 IU/L
- 25 IU/L
- 50 IU/L

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Running the Model

- 10,000 “subjects” per analysis
  - Results are averaged across all 10,000
  - Results are average for entire population, not just those of childbearing potential
    - Model-estimated proportion childbearing potential
      - Acne: 99.0%
      - Epilepsy: 87.6%
      - Depression: 73.4%
      - Rheumatoid Arthritis: 51.1%

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Running the Model

- For illustrative purposes
  - One time screen, random day
  - One time screen, 1st week after expected menses
  - Screen, repeat every 30 days, random day
  - Screen, repeat every 30 days, 1st week after expected menses

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Results

- Meant to illustrate potential application of model
- Some additional revisions needed
- Output
  - Total pregnancies
  - Test detected pregnancies
  - False-negative and false-positive results
- More detailed output possible (e.g., gestational age of pregnancy at time of detection)

CLINICAL TRIALS TRANSFORMATION INITIATIVE

At Initial Screen, Random Day

OUTCOME	Acne		Epilepsy		Depression		RA	
Pregnancies	1.47%		0.8%		0.47%		0.22%	
Undetected Pregnancies	Random	Timed	Random	Timed	Random	Timed	Random	Timed
5 IU/L	1.0%	*0.47%*	0.59%	*0.33%*	0.36%	*0.17%*	0.22%	*0.01%*
20 IU/L	1.02%	*0.9%*	0.64%	*0.54%*	0.39%	*0.31%*	0.18%	*0.14%*
25 IU/L	1.05%	*0.95%*	0.66%	*0.58%*	0.40%	*0.34%*	0.19%	*0.16%*
50 IU/L	1.18%	*1.24%*	0.73%	*0.76%*	0.43%	*0.43%*	0.22%	*0.27%*
Screen Detected Pregnancies								
5 IU/L	0.5%	*0.86%*	0.31%	*0.43%*	0.13%	*0.34%*	0.04%	*0.19%*
20 IU/L	0.19%	*0.49%*	0.12%	*0.31%*	0.06%	*0.18%*	0.05%	*0.16%*
25 IU/L	0.16%	*0.44%*	0.10%	*0.27%*	0.05%	*0.15%*	0.04%	*0.14%*
50 IU/L	0.03%	*0.14%*	0.03%	*0.09%*	0.02%	*0.06%*	0.01%	*0.03%*
False Positives								
5 IU/L	0.02%	*0%*	0.1%	*0.11%*	0.13%	*0.16%*	0.15%	*0.13%*
20 IU/L	0%	*0%*	0%	*0%*	0%	*0%*	0%	*0%*
25 IU/L	0%	*0%*	0%	*0%*	0%	*0%*	0%	*0%*
50 IU/L	0%	*0%*	0%	*0%*	0%	*0%*	0%	*0%*

TRANSFORMATION INITIATIVE

Screen and q 30 days, random

OUTCOME	Acne	Epilepsy	Depression	RA
Pregnancies	6.57%	4.15%	2.63%	1.23%
5 IU/L	5.56%	3.35%	2.43%	0.92%
20 IU/L	6.31%	4.02%	2.49%	1.19%
25 IU/L	6.34%	4.01%	2.51%	1.17%
50 IU/L	6.45%	4.07%	2.55%	1.20%
Test-detected pregnancies				
5 IU/L	0.47%	0.26%	0.22%	0.07%
20 IU/L	0.21%	0.13%	0.09%	0.04%
25 IU/L	0.18%	0.11%	0.09%	0.04%
50 IU/L	0.11%	0.03%	0.04%	0.04%
False Positives				
5 IU/L	0.24%	0.87%	0.8%	1.0%
20 IU/L	0%	0%	0%	0%
25 IU/L	0%	0%	0%	0%
50 IU/L	0%	0%	0%	0%

Qualitative Results

- Probability of pregnancy dependent on age distribution of subjects
- Difference between threshold of 5 and 20 has implications for positive and negative predictive value, which varies by age
- Timing of testing relative to menses increases detection

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Would Further Development of this Model be Useful?

- Ability to incorporate
  - Different age structure
  - Different contraceptive mixes
  - Different study durations
  - Different frequency of follow-up testing
- What outputs most useful?
- Prepopulated results or interactive?
- Other considerations?

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