# Debating the Pros and Cons of PGD

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# PGT-A:
# Knowledge Gaps and Challenges

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# Disclosures

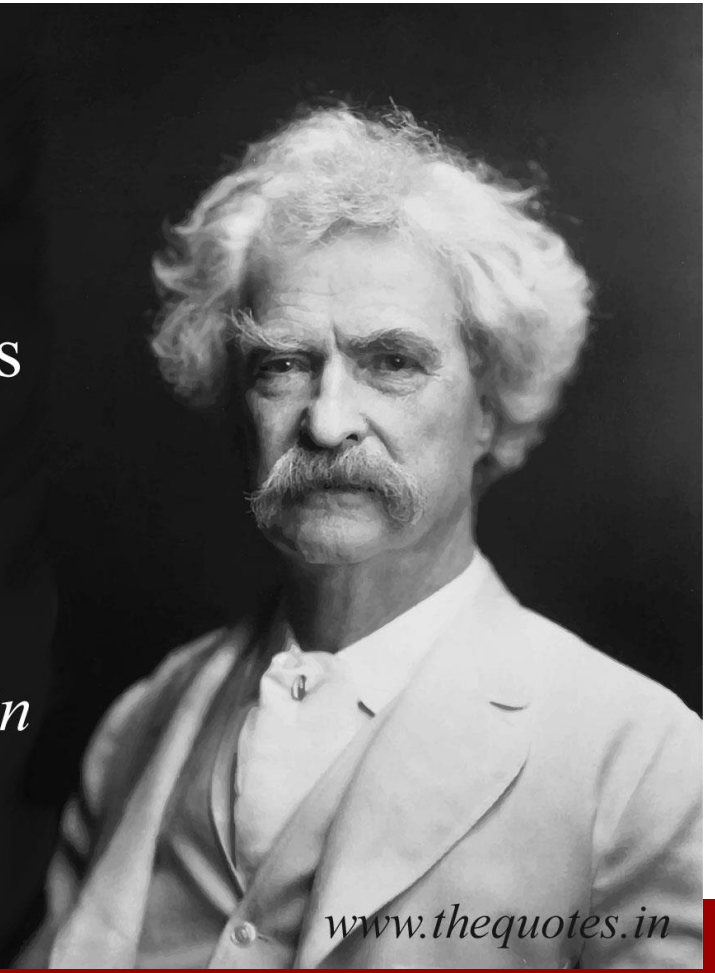
- ASRM
- No commercial affiliations

# Learning Objectives

1) To describe limitations and knowledge gaps in PGT-A
2) To understand the challenges of further PGT-A investigations
3) To counsel patients about the appropriate application of PGT-A

It ain't what you don't know that gets you into trouble. It's what you know for sure that just ain't so.

*Mark Twain*

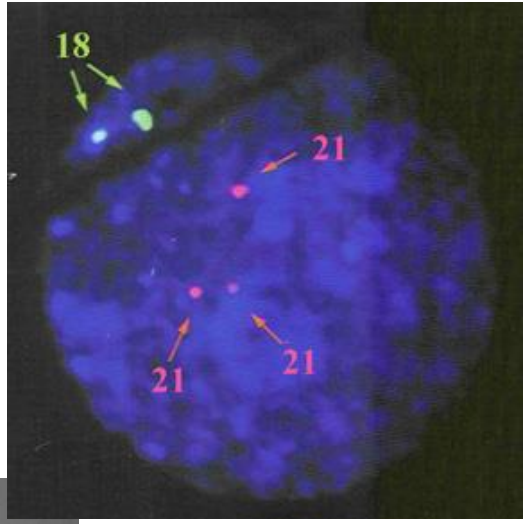


# Why are we still debating this?

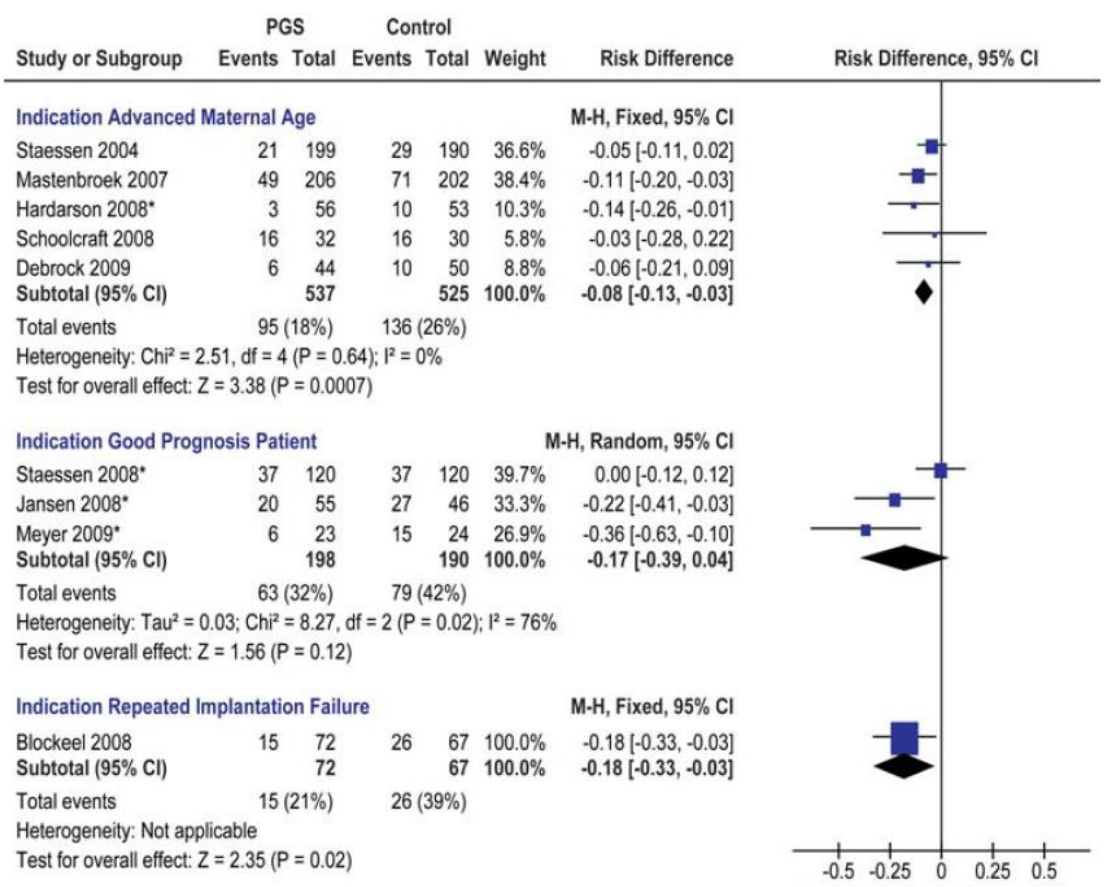
- Numbers are not consistent
- Aneuploidy
  - Unclear rate
- Mosaicism
  - Unclear incidence in blastocysts (and cleavage stage)
  - Unclear effect on accuracy of embryo biopsy
- Unknown damage from embryo biopsy

# PGT-A (PGS) 1.0

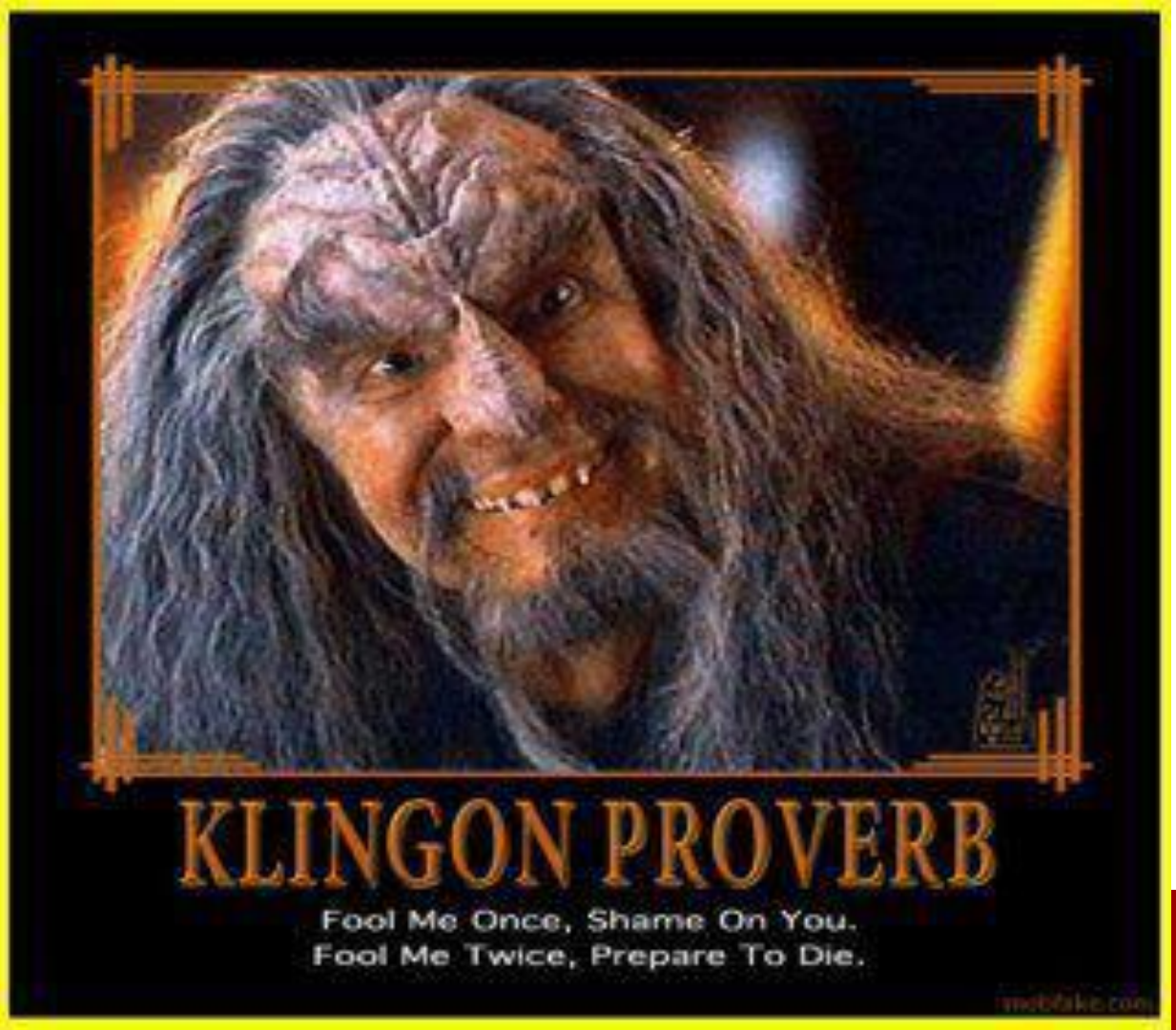
- Cleavage stage biopsy
- FISH analysis
- Widely utilized




# PGS 1.0 meta-analysis




Mastenbroek et al, Human Reprod Update 2011;4:454


KLINGON PROVERB
Fool Me Once, Shame On You.
Fool Me Twice, Prepare To Die.

# Intuitive appeal of PGS

- Additional information
  - Why would you NOT want that???
- Practically
  - Why would I want to transfer an aneuploid embryo?
- Theoretically:
  - Faster time to pregnancy
  - Decreased miscarriage rate

# Pressure to perform PGT-A

- Natural appeal of new technology
  - Must be better
- Pressure from consumers
- Pressure from registry
  - Need to optimize outcome of 1$^{st}$ embryo transfer

# Gaps in Knowledge

- Biology of the pre-implantation human embryo
  - Rapid division, especially in the trophectoderm
    - Multi-nucleated cells, ?resemble sycytiotrophoblast
    - Predisposed to mosaicism, aneuploidy?
- True incidence of chromosomal abnormalities
  - Aneuploidy, mosaicism
  - Correlation between trophectoderm and inner cell mass
- Embryo biopsy
  - Extent of damage to the embryo

# What does screening with PGT-A tell us?

- Information about the genetic make-up of the embryo
  - Improved selection of the 1st embryo transfer
  - Increase in implantation rate of 1st embryo
- No improvement in embryo quality
  - No increase in cumulative pregnancy rate per aspiration
  - Any error/damage must cause decrease in cumulative pregnancy rate

# Inherent down-sides of PGT-A

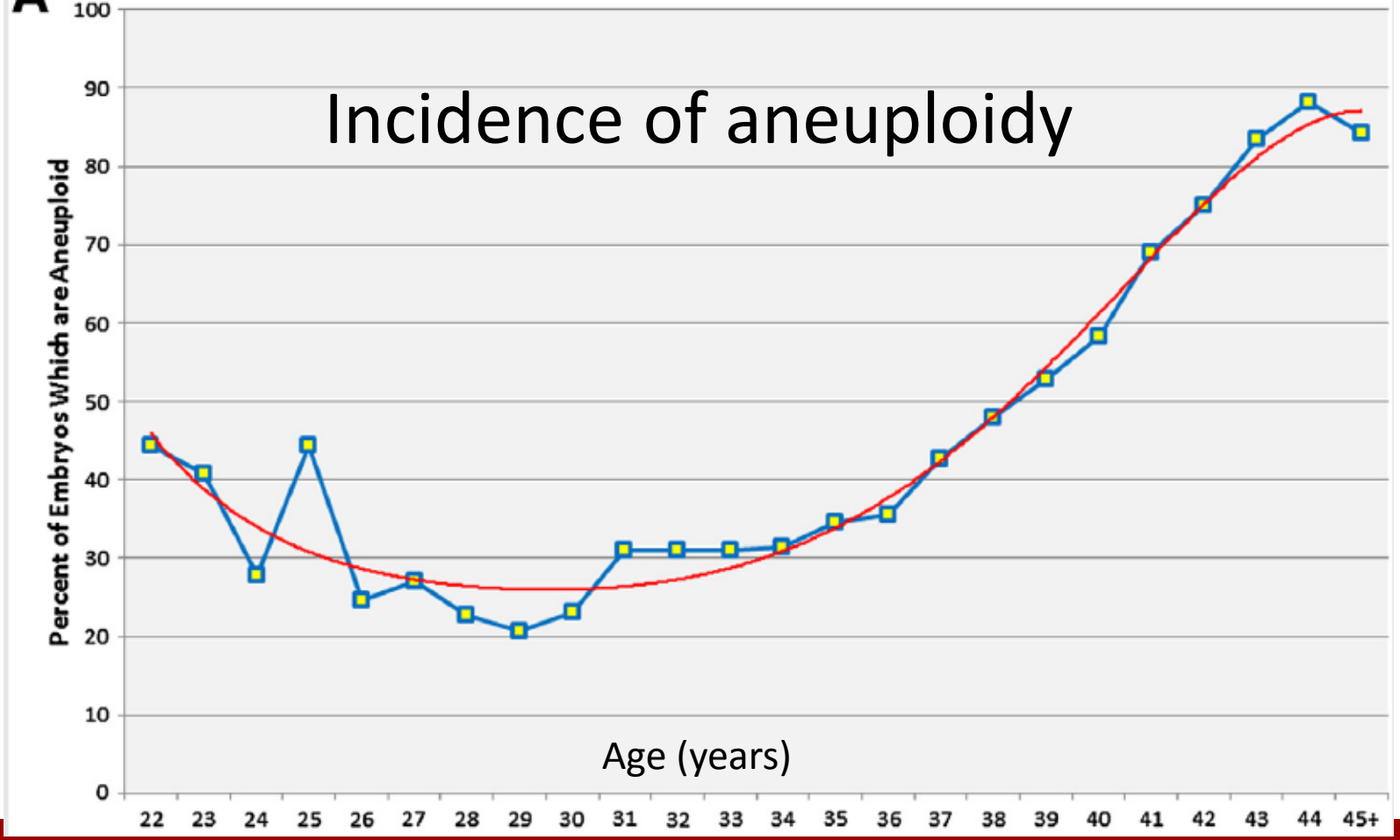
- Blastocyst culture
- Accuracy of testing
  - Error in testing: lab tests are not perfect
  - Inherent error: mosaicism (biopsy not representative) of rest of embryo
- Trauma from embryo biopsy
- Loss of potential live births
  - Discarding or damage to normal embryos

# Blastocyst vs Cleavage stage transfer

- Issue is NOT settled
- Increased implantation rate with blastocyst
- No increase when frozen embryos considered
- No stratification by age
  - Difference between 32 yo and 42 yo
  - Is cleavage stage better for older women?

Glujovsky, Cochrane Database 2016:6, CD002118

# Incidence of aneuploidy




Franasiak et al, Fertil Steril 2014;101;656

# Incidence of euploidy (based on age and # of embryos)

| | Egg Donor | <35 | 35-37 | 38-40 | 41-42 | >42 |
|---|---|---|---|---|---|---|
| 1-3 embryos | 59 | 56 | 47 | 36 | 23 | 14 |
| 4-6 embryos | 62 | 55 | 48 | 36 | 24 | 16 |
| 7-10 embryos | 64 | 57 | 49 | 37 | 23 | 15 |
| >10 embryos | 66 | 58 | 50 | 38 | 26 | 24 |
| Total | 64 | 57 | 49 | 37 | 24 | 16 |

CooperGenomics

| Maternal age | Risk of Down's Syndrome | Risk of all chromosomal abnormalities |
|---|---|---|
| 33 | 1/416 | 1/208 |
| 34 | 1/333 | 1/151 |
| 35 | 1/250 | 1/132 |
| 36 | 1/192 | 1/105 |
| 37 | 1/149 | 1/83 |
| 38 | 1/115 | 1/65 |
| 39 | 1/89 | 1/53 |
| 40 | 1/69 | 1/40 |
| 41 | 1/53 | 1/31 |
| 42 | 1/41 | 1/25 |
| 43 | 1/31 | 1/19 |
| 44 | 1/25 | 1/15 |
| 45 | 1/19 | 1/12 |

Hook et al. JAMA 1983.

# Accuracy of testing?

## Comprehensive chromosome screening is highly predictive of the reproductive potential of human embryos: a prospective, blinded, nonselection study

Richard T. Scott Jr., M.D.,[a,b] Kathleen Ferry, B.S.,[a] Jing Su, M.S.,[a] Xin Tao, M.S.,[a] Katherine Scott, M.S.,[a] and Nathan R. Treff, Ph.D.[a,b]

NCT 01219517
NCT 01219504

Scott et al, Fertil Steril 2012;97:870

# Predictive Value of CCS

- 255 embryos biopsied
  - Average age = 34
    - 113 cleavage, 142 trophectoderm
      - 12 failed to amplify,
      - 11 nonconcurrent copy assignments (?)
  - 232 evaluable microarray results
    - 133 euploid
      - 55 (41.4%) of these resulted in normal children
    - 99 (42.7%) aneuploid
      - 4 (4%) normal children **(96% negative predictive value)**

Scott et al, Fertil Steril 2012;97:870

| | Implantation | No implantation | |
|---|---|---|---|
| Euploid | 55 | 78 | 133 |
| Aneuploid | 4 | 95 | 99 |
| | 59 | 173 | 232 |

41% of the “Euploid” group implanted

4% of the “Aneuploid” group implanted

Error rate: 10/99 (10%) “aneuploid” were actually euploid

4/59 (6.8%) implantations would have been discarded

Scott et al, Fertil Steril 2012;97:870

# Trauma from Embryo Biopsy?

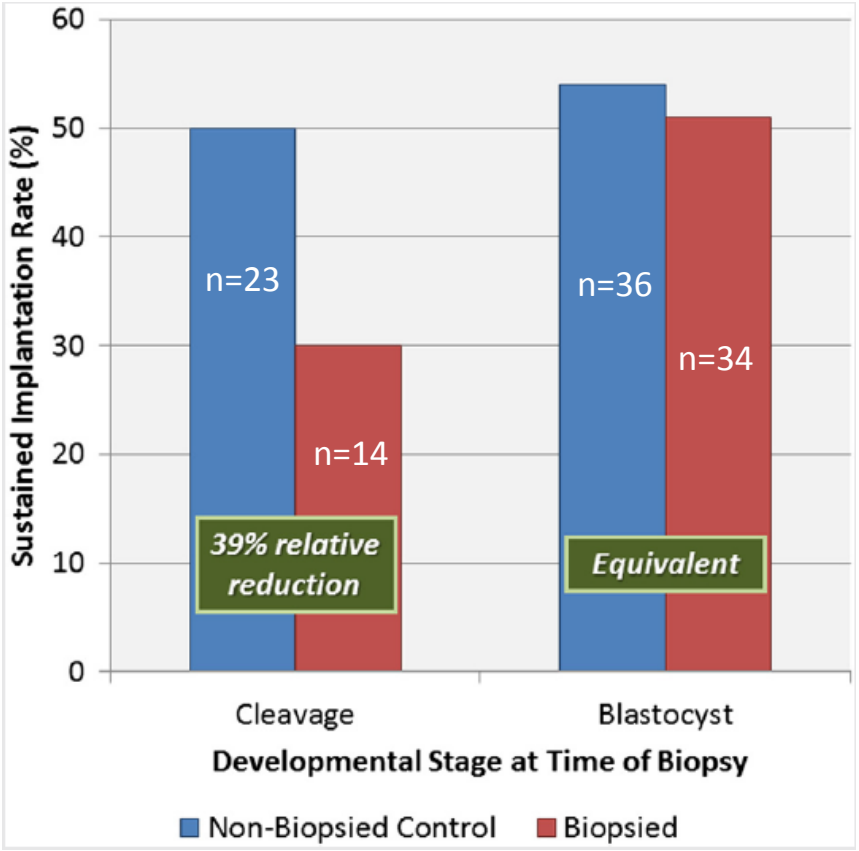
## Cleavage-stage biopsy significantly impairs human embryonic implantation potential while blastocyst biopsy does not: a randomized and paired clinical trial

Richard T. Scott Jr., M.D.,[a,b] Kathleen M. Upham, B.S.,[a] Eric J. Forman, M.D.,[b] Tian Zhao, M.S.,[a] and Nathan R. Treff, Ph.D.[a,b,c]

"Seminal Contribution"

NCT 01219504

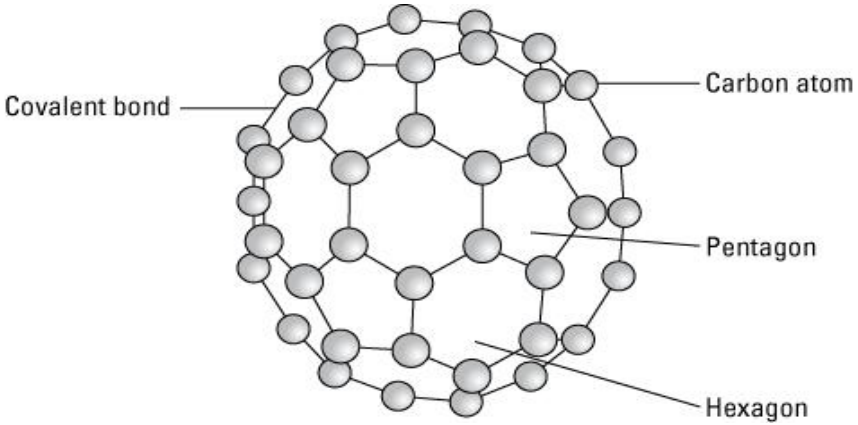
Scott et al, Fertil Steril 2013;100:624




- All patients < 35 yo
  - Good ovarian reserve
- ET within 3 hours of Bx
  - All 4AA – 4BB
  - Without knowledge of ploidy
- Blastocysts (n=67)
  - No ↓ in implantation rate
  - 54% vs 51%
    - 30/69 aneuploid (42.7%)
- Cleavage stage (n=46)
  - 39% ↓ in implantation rate
    - 19 aneuploid (41.3%)
- Can these results be extrapolated to women > 40?

Scott et al, Fertil Steril 2013;100:624

# What does a day 5 embryo look like?




- "Buckyball"
  - Naturally occurring $C_{60}$
    - 32 faces
      - 20 hexagons
      - 12 pentagons
  - Trophectoderm with 64 cells
    - 2 cells/face
  - Imagine removing 5 cells
    - Is this really NOT traumatic?

# How many embryos do we lose?

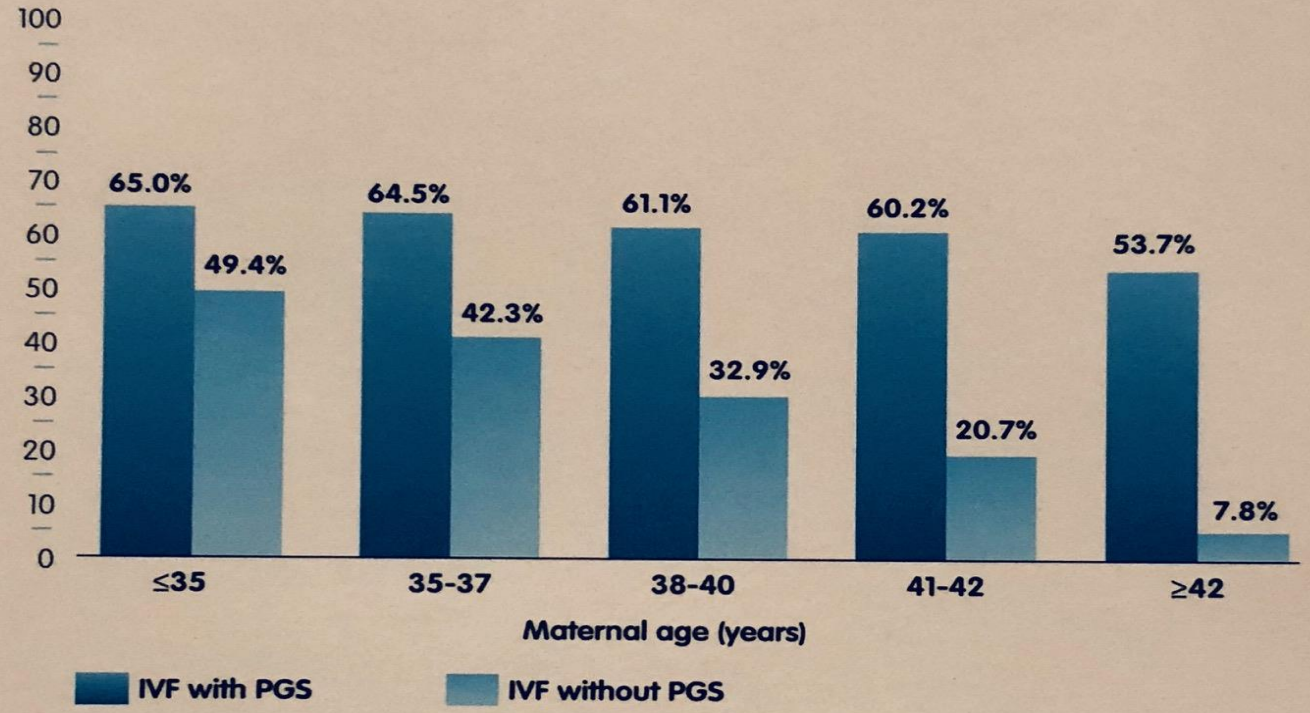
- Best-case scenario
- Good prognosis patient
  - Under 35
  - Expected aneuploidy rate?
  - Implantation rate with and without PGT-A?

# Incidence of euploidy (based on age and # of embryos)

| No. of day 5 embryos | Patient Age | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | <35 | | 35-37 | | 38-40 | | 40+ | |
| | **Euploid** | Patients | **Euploid** | Patients | **Euploid** | Patients | **Euploid** | Patients |
| 1-3 embryos | **54%** | 29% | **50%** | 33% | **38%** | 44% | **24%** | 56% |
| 4-6 embryos | **57%** | 32% | **47%** | 35% | **36%** | 34% | **26%** | 28% |
| 7-9 embryos | **55%** | 22% | **49%** | 20% | **38%** | 14% | **28%** | 11% |
| 10+ embryos | **52%** | 17% | **46%** | 12% | **35%** | 8% | **28%** | 5% |

igenomix
PIONEERS IN REPRODUCTIVE GENETICS

# Ongoing pregnancy rate per blastocyst transfer

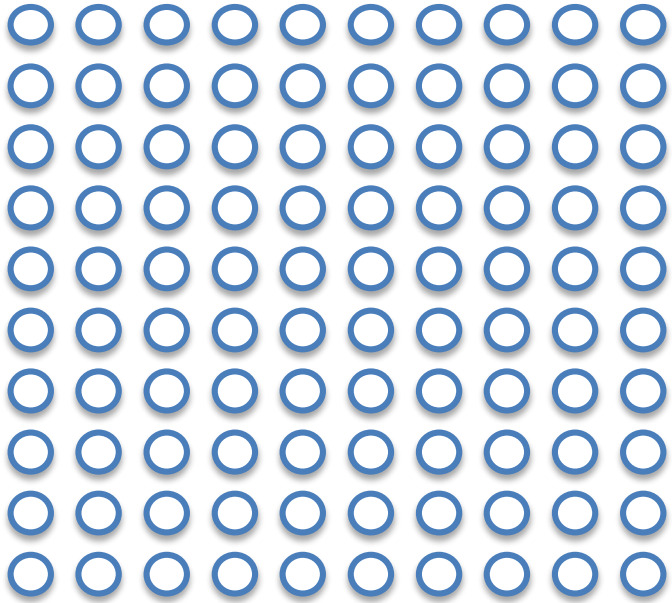



*Internal IGENOMIX data 2016 based on outcomes and 2015 SART data.

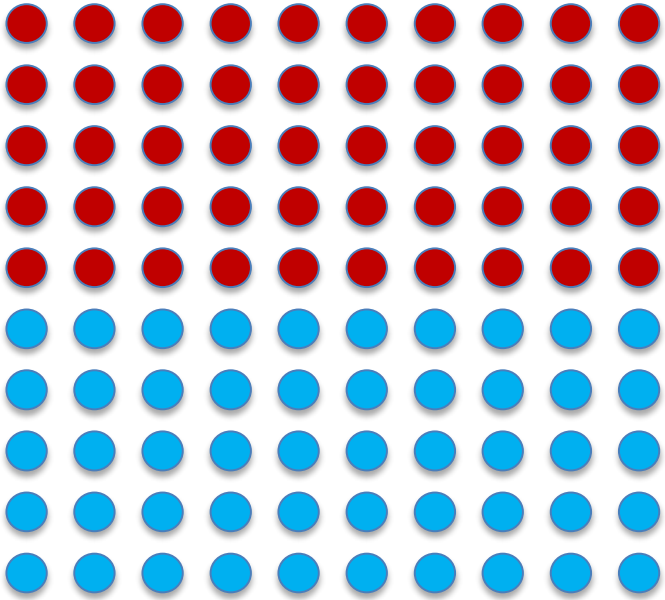
# How many embryos do we lose?

- Typical good prognosis patient
  - PGS testing
    - 40% aneuploidy
  - 50% implantation rate before testing
  - 65% implantation rate after testing

# 100 embryos



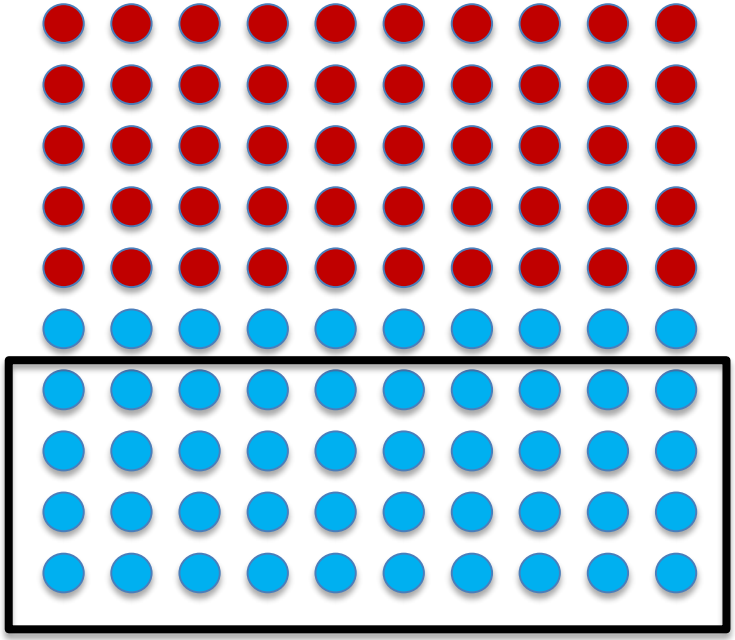
# 100 embryos, 50% implantation rate



50 implant

50 no implant

# 100 embryos, 50% implantation rate
# 40% aneuploidy

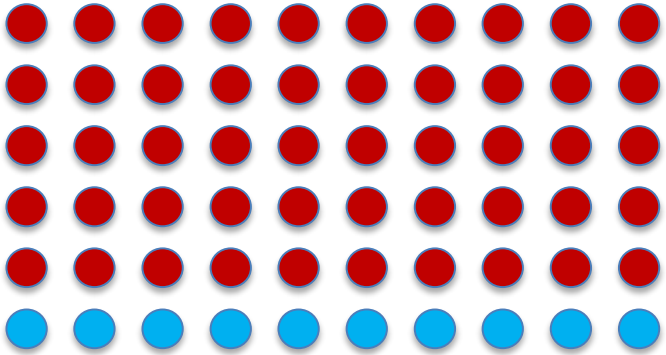


50 implant

50 no implant

40 aneuploid

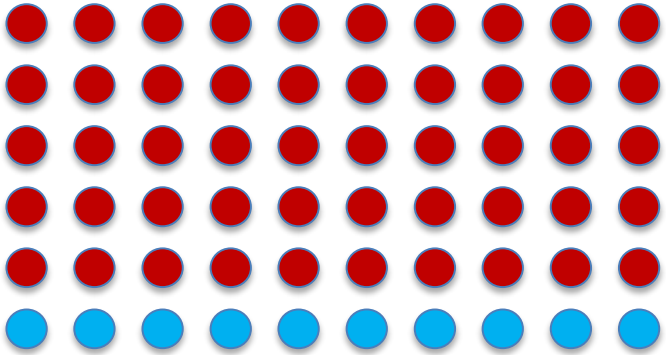
# 100 embryos, 50% implantation rate
# 40% aneuploidy



50 implant

10 no implant

# 100 embryos, 50% implantation rate
# 40% aneuploidy



50 implant

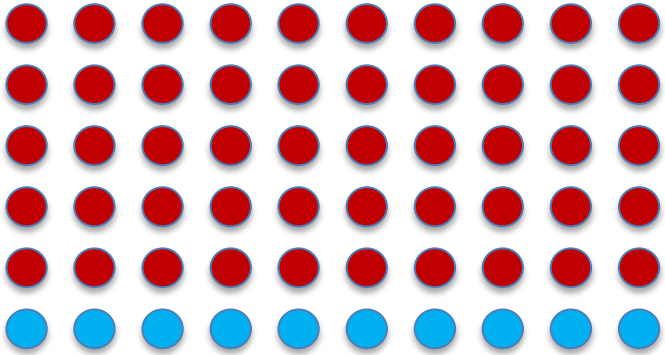
10 no implant

After PGS, 60 embryos left

New implantation rate:

50/60 = 83.3%

# 100 embryos, 50% implantation rate
# 40% aneuploidy



50 implant

10 no implant

After PGS, 60 embryos left

New implantation rate:

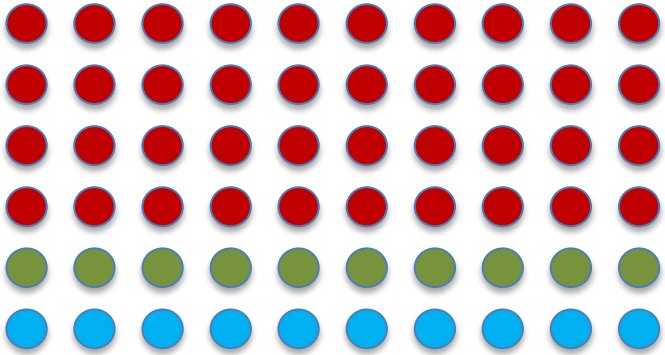
50/60 = 83.3%

Actual implantation rate is:

65% ≈ 40/60

Improvement over 50%

# 100 embryos, 50% implantation rate
# 40% aneuploidy



40 implant

10 no implant

After PGS, 60 embryos left

New implantation rate:

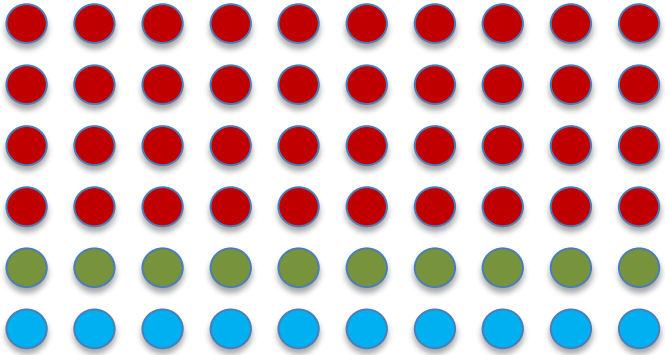
50/60 = 83.3%

Actual implantation rate is:

65% ≈ 40/60

Improvement over 50%

# 100 embryos, 50% implantation rate
# 40% aneuploidy



40 implant

10 (20%) lost

10 no implant

After PGS, 60 embryos left

New implantation rate:

50/60 = 83.3%

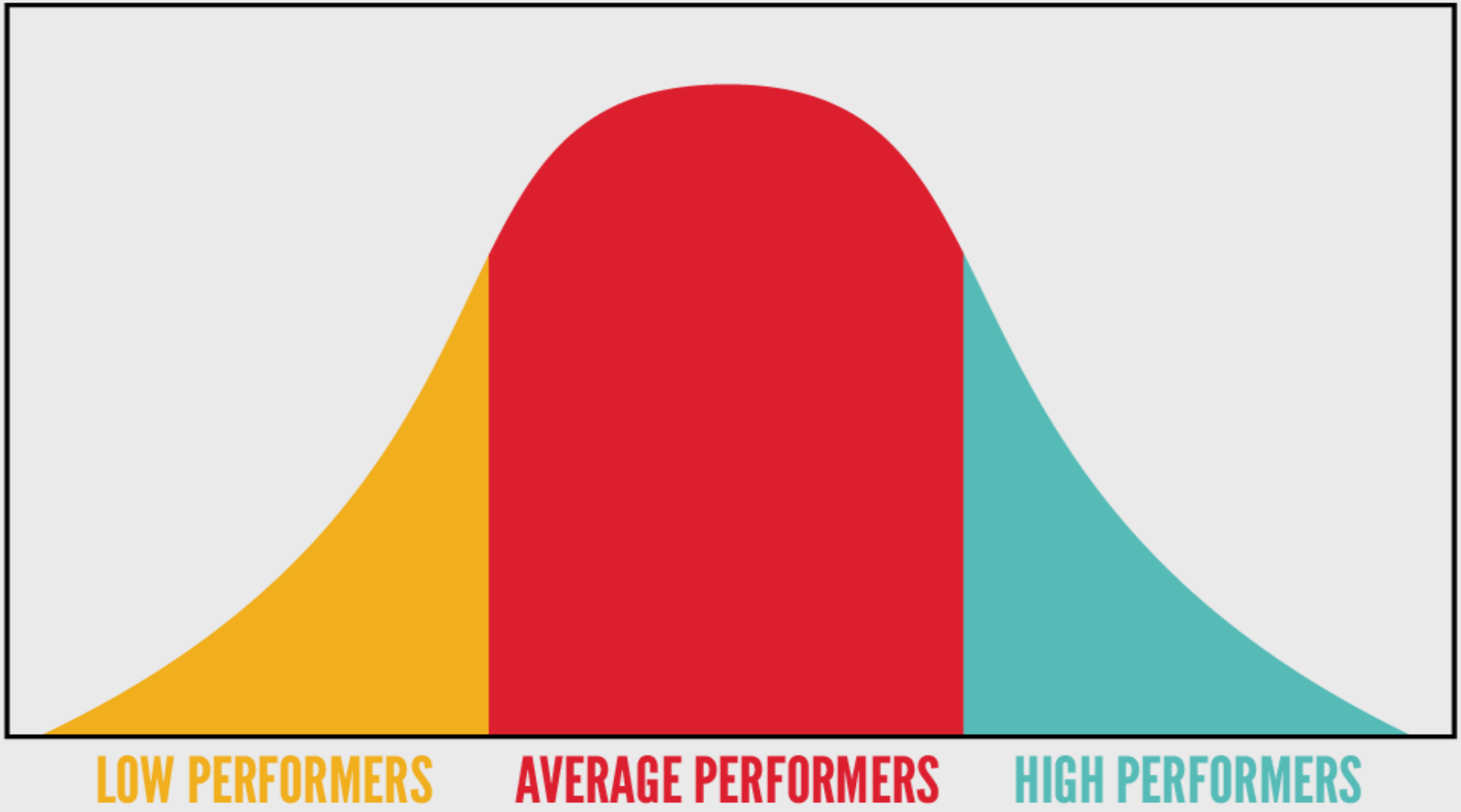
Actual implantation rate is:

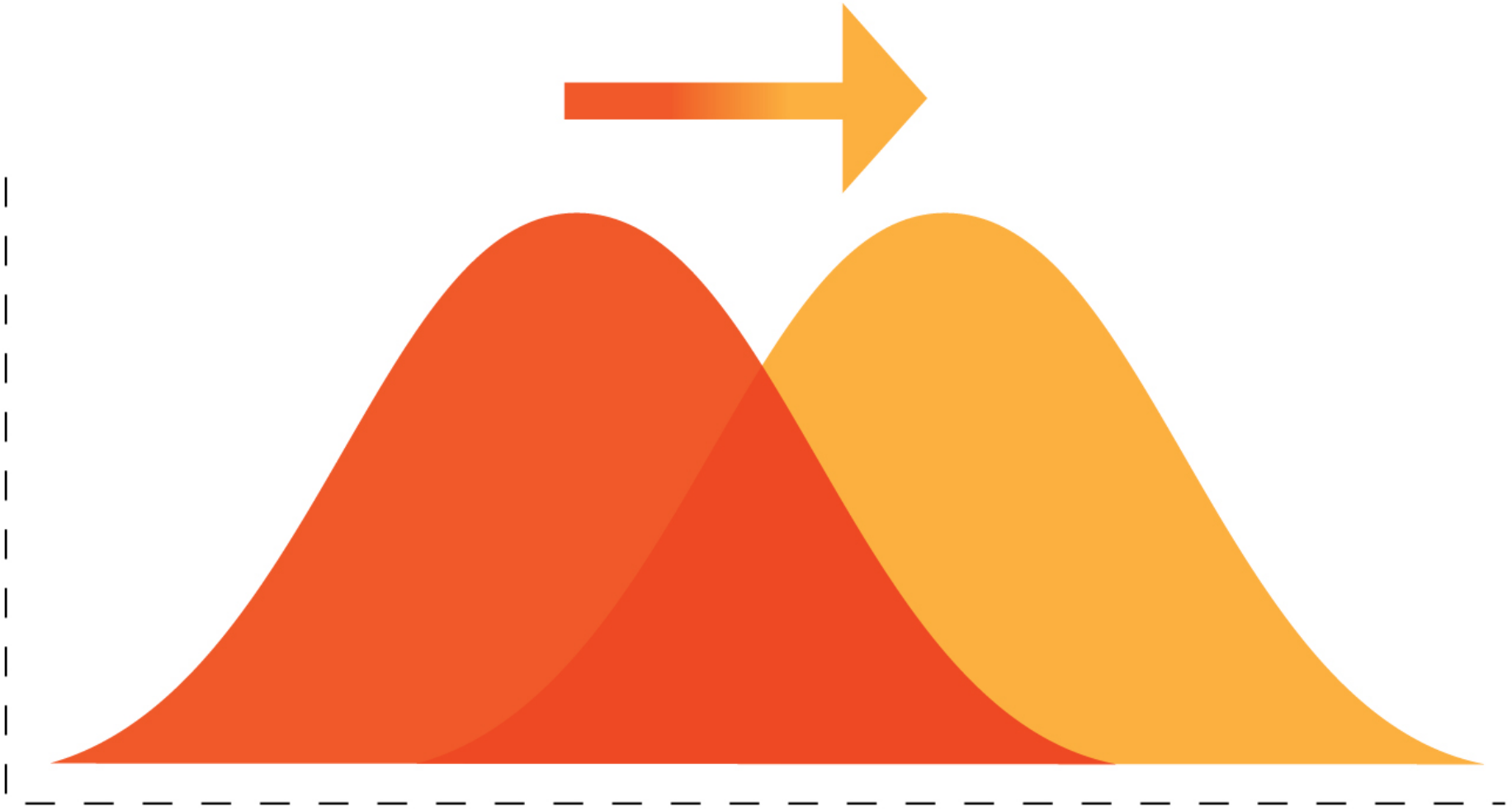
65% ≈ 40/60

Improvement over 50%

# General principle

- When we remove from the cohort a sub-group which has a lower incidence of a given characteristic, the average of that characteristic in the remaining group must increase.
- Age
- Height
- Implantation rate


LOW PERFORMERS
AVERAGE PERFORMERS
HIGH PERFORMERS



# Generalized Efficiency Equation

Embryo implantation (EI) must increase if we are removing lower quality embryos from the population

EI (expected) = EI (untested) / (percent normal)

Efficiency = EI (observed after testing) / EI (expected)

% embryos lost = 1 - Efficiency

# Generalized Efficiency Equation

- Previous example:
  - 50% (untested) / (60% normal) = 83.3% (expected)
  - Efficiency = 65% (observed) / 83.3% (expected)
    = 0.80
  - % embryos lost = 1 – 0.80 = 0.20

# When is it OK to lose 20% of implantations?

- Specific reason for genetic diagnosis
- Excellent prognosis patient
  - More embryos than she needs

# When is it NOT OK to lose 20%?

- Limited number of eggs
  - Fertility preservation patients
  - Patients over 40

# What are actual “real life” implantation rates?

- SART CORS registry
- Query the database = “filter” function

www.sartcorsonline.com/rptCSR_PublicMultYear.aspx?reportingYear=2014

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UNDERSTAND THIS REPORT | PATIENT'S OWN EGGS | DONOR

Cumulative Outcome Per Egg Retrieval Cycle | Primary Outcome Per Egg Retrieval Cycle | Subsequent Outcome (Frozen Cycles) | Live

PATIENT'S OWN EGGS

## PRELIMINARY PRIMARY OUTCOME PER EGG RETRIEVAL CYCLE

| | Age of woman | | | |
|---|---|---|---|---|
| | < 35 | 35 - 37 | 38 - 40 | 41 - 42 |
| Number of cycle starts | 42728 | 22675 | 22101 | 11899 |
| **Singletons** | **31.9 %** | **24.7 %** | **16.7 %** | **8.7 %** |
| Twins | 8.8 % | 6.0 % | 3.3 % | 1.2 % |
| Triplets or more | 0.2 % | 0.1 % | 0.1 % | 0.0 % |
| Live Births | 40.9 % | 30.9 % | 20.1 % | 9.9 % |
| (Confidence Range) | (40.4 - 41.4) | (30.3 - 31.5) | (19.6 - 20.6) | (9.4 - 10.4) |
| Term | 78.2 % | 79.4 % | 80.2 % | 81.1 % |
| Pre-term | 17.9 % | 16.9 % | 16.3 % | 15.2 % |
| Very pre-term | 3.9 % | 3.7 % | 3.5 % | 3.7 % |

## Filter Report

Filters other than Reporting Year cannot be applied to the 'Cumulative Outcome Per Intended Egg Retrieval' and 'Live Birth Per Patient' sections. These sections will be hidden if a filter has been applied.

**Reporting Year**

2014

Cycle Type

| All cycle types |
| --- |
| Minimal stimulation |
| Natural cycle |
| Conventional stimulation |
| In vitro maturation |

Diagnosis

All Diagnoses

Additional Filters

| | Include Only | Exclude |
| --- | --- | --- |
| First IVF | ☐ | ☐ |
| eSET | ☑ | ☐ |
| PGD / PGS | ☐ | ☑ |
| Day 5/6 transfer | ☐ | ☐ |
| Frozen egg | ☐ | ☐ |
| Frozen embryo | ☐ | ☐ |
| Gestational carrier | ☐ | ☐ |
| ICSI | ☐ | ☐ |

Apply filter | Reset filter | Cancel

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Cumulative Outcome Per Egg Retrieval Cycle | Primary Outcome Per Egg Retrieval Cycle | Subsequent Outcome (Frozen Cycles) | Liv

PATIENT'S OWN EGGS

## FINAL PRIMARY OUTCOME PER EGG RETRIEVAL CYCLE

| | Age of woman | | | |
|---|---|---|---|---|
| | < 35 | 35 - 37 | 38 - 40 | 41 - 42 |
| Number of cycle starts | 10048 | 2876 | 1194 | 316 |
| **Singletons** | **50.0 %** | **42.7 %** | **31.3 %** | **21.8 %** |
| Twins | 0.8 % | 0.5 % | 0.1 % | 0.9 % |
| Triplets or more | 0.0 % | 0 % | 0 % | 0 % |
| Live Births | 50.8 % | 43.1 % | 31.4 % | 22.8 % |
| (Confidence Range) | (49.8 - 51.8) | (41.3 - 44.9) | (28.8 - 34.0) | (18.2 - 27.4) |
| Term | 89.1 % | 88.7 % | 86.7 % | 77.8 % |
| Pre-term | 9.1 % | 9.6 % | 10.7 % | 19.4 % |
| Very pre-term | 1.8 % | 1.7 % | 2.7 % | 2.8 % |

# Filter Report

Filters other than Reporting Year cannot be applied to the 'Cumulative Outcome Per Intended Egg Retrieval' and 'Live Birth Per Patient' sections. These sections will be hidden if a filter has been applied.

**Reporting Year**

2014

Diagnosis

All Diagnoses

Cycle Type

| All cycle types |
| --- |
| Minimal stimulation |
| Natural cycle |
| Conventional stimulation |
| In vitro maturation |

Additional Filters

| | Include Only | Exclude |
| --- | --- | --- |
| First IVF | ☐ | ☐ |
| eSET | ☑ | ☐ |
| PGD / PGS | ☑ | ☐ |
| Day 5/6 transfer | ☐ | ☐ |
| Frozen egg | ☐ | ☐ |
| Frozen embryo | ☐ | ☐ |
| Gestational carrier | ☐ | ☐ |
| ICSI | ☐ | ☐ |

Apply filter | Reset filter | Cancel

www.sartcorsonline.com/rptCSR_PublicMultYear.aspx?reportingYear=2014

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PATIENT'S OWN EGGS

## FINAL PRIMARY OUTCOME PER EGG RETRIEVAL CYCLE

| | Age of woman | | | |
|---|---|---|---|---|
| | **< 35** | **35 - 37** | **38 - 40** | **41 - 42** |
| Number of cycle starts | 2047 | 1311 | 1219 | 418 |
| **Singletons** | **49.9 %** | **52.6 %** | **52.0 %** | **49.8 %** |
| Twins | 0.8 % | 0.5 % | 0.3 % | 2.2 % |
| Triplets or more | 0 % | 0 % | 0 % | 0.2 % |
| Live Births | 50.7 % | 53.1 % | 52.3 % | 52.2 % |
| (Confidence Range) | (48.5 - 52.8) | (50.4 - 55.8) | (49.5 - 55.1) | (47.4 - 56.9) |
| Term | 88.1 % | 90.9 % | 88.6 % | 89.0 % |
| Pre-term | 9.5 % | 7.8 % | 9.7 % | 9.2 % |
| Very pre-term | 2.4 % | 1.3 % | 1.7 % | 1.8 % |

# Generalized Efficiency Equation

- "Real world" example:
  - 50% (untested) / (60% normal) = 83.3% (expected)
  - Efficiency = 50% (observed) / 83.3% (expected)
    = 0.60
  - % embryos lost = 1 – 0.60 = 0.40

# Counseling patients about PGT-A

- PGT-A will provide information about the embryo
- PGT-A will likely increase implantation in 1st ET
- PGT-A will add cost
- You will lose 20% - 40% of embryos that might have implanted
- Cumulative pregnancy rate will be decreased

# Conclusions – PGT-A

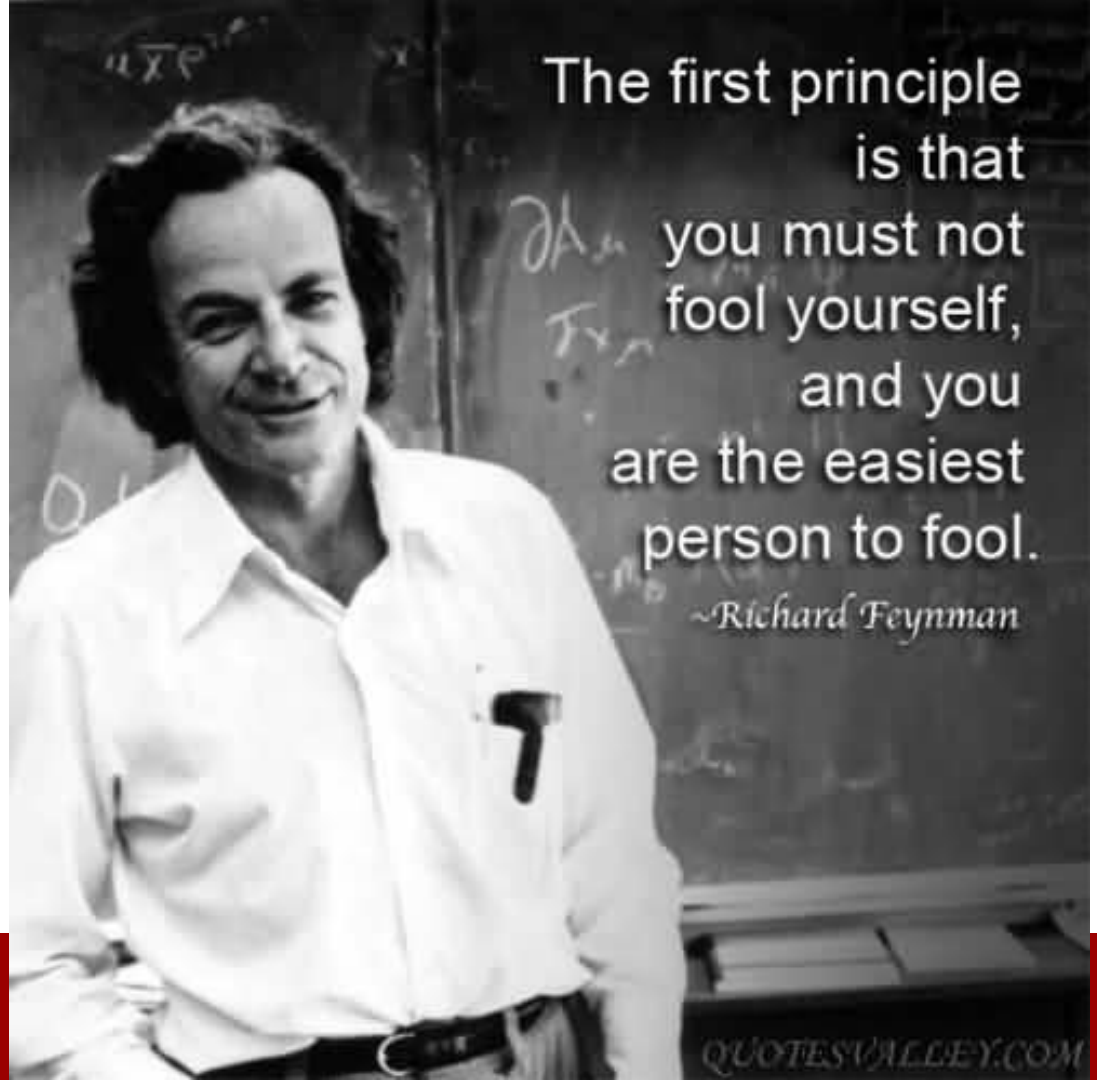
- Useful:
  - Specific diagnosis, e.g. translocation, sex selection
  - Recurrent aneuploidy (RPL) (likely)
  - Age 36-39, with many blastocysts
- Unnecessary:
  - Young good prognosis patients (< 35 yo)
- Not worth it:
  - Limited number of eggs
    - Fertility preservation, women over 40

# Incidence of Mosaicism

- Confined placental mosaicism
  - 1-2%
- ?Incidence in embryos
  - Up to 75% in cleavage stage
  - Up to 20% in blastocysts
- ?impact on implantation rates
- ?interpretation of PGS results

# Challenges in PGT

- Biology of the pre-implantation human embryo
  - Rapid division, especially in the trophectoderm
  - Unique life form
- True incidence of chromosomal content
  - Aneuploidy, mosaicism
  - Significance of trophectoderm aneuploidy
- Embryo biopsy
  - Invasive


The first principle
is that
you must not
fool yourself,
and you
are the easiest
person to fool.
~Richard Feynman
QUOTESVALLEY.COM

Thank you