LEARNING OBJECTIVES

At the conclusion of this presentation, participants should be able to:

1) Describe the chances of chromosomally unbalanced offspring in carrier couples with RPL

2) Describe the psychological impact of receiving abnormal genetic test results

3) Realize that you can change clinical management

DISCLOSURE

- None
Eliminating Waste in US Health Care

Donald M. Berwick, MD, MPP
Andrew W. Hackbarth, MPH

No matter how polished policies in the United States have become, nearly everyone agrees that health care costs are unsustainable. At least 30% of the gross domestic product (GDP) in 2011, priced for 20% by 2020,[1] the nation’s increasing health care expenditures reduce the resources available for other worthy government programs, crowd wages, and undermine the competitiveness of US industry. Although Medicare and Medicaid are often in the crossfire, the health care cost problems affect the private sector just as much.

The need is urgent to bring US health care costs into a sustainable range for both public and private payers. Commonly, programs to contain costs use interventions, such as reductions in payment levels, benefit structures, and eligibility. A less harmful strategy would reduce waste, not value-added care. The opportunity is enormous. In just 6 categories of waste—over-treatment, failures of care coordination, failures in execution of care processes, administrative complexity, pricing failures, and fraud and abuse—the sum of the lowest available estimates exceed 20% of total health care expenditures. The actual total may be far greater. The savings potentially achievable from systematic, comprehensive, and cooperative pursuit of even a fractional reduction in waste are far higher than from more direct and blunt cuts in care and coverage. The potential economic dislocations, however, are severe and require mitigation through careful transition strategies.

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Published online February 14, 2012. See also: [jama.com]

THE FUTURE IS OURS
PARENTAL KARYOTYPING

- 1962: This now belongs to the past
- 1980: This now belongs to the past
- 1990:

SELECTIVE KARYOTYPING MODEL

Refrain from karyotyping in low risk couples
Savings: 33%

TWO LARGE NATION WIDE STUDIES ON KARYOTYPING FOR RPL

<table>
<thead>
<tr>
<th>Author/ Country/ Type of study</th>
<th>balanced carrier status n/N</th>
<th>Follow-up period</th>
<th>unbalanced structural chr abnorm (PND)</th>
<th>Children born with unbalanced str chr abn</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barber UK 2010 Retrospective cohort study</td>
<td>406/20,432 individuals (1.9%)</td>
<td>5-30 yrs (range)</td>
<td>4</td>
<td>Not reported</td>
</tr>
<tr>
<td>Franssen NL 2006 Index control study</td>
<td>382/11,971 couples (3.2%) (1.6% individuals)</td>
<td>5.8 yrs (mean)</td>
<td>4/150 pregnancies in 278 couples*</td>
<td>2*</td>
</tr>
</tbody>
</table>

* 278/382 carrier couples participated

Barber BJOG 2010, Franssen BMJ 2006
**CUMULATIVE REPRODUCTIVE OUTCOMES**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Carriers (n = 207)</th>
<th>Controls (n = 409)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failure to conceive</td>
<td>8 (3%)</td>
<td>19 (5%)</td>
</tr>
<tr>
<td>Miscarriage</td>
<td>120 (49%)</td>
<td>122 (10%)*</td>
</tr>
<tr>
<td>Terminated pregnancy</td>
<td>6 (2%)</td>
<td>8 (2%)</td>
</tr>
<tr>
<td>Ectopic pregnancy</td>
<td>3 (1%)</td>
<td>13 (3%)</td>
</tr>
<tr>
<td>Stillbirth</td>
<td>3 (1%)</td>
<td>6 (2%)</td>
</tr>
<tr>
<td>Post-partum deceased child</td>
<td>1 (0.4%)</td>
<td>4 (1%)</td>
</tr>
<tr>
<td>Ill/ handicapped child</td>
<td>2 (1%)</td>
<td>11 (3%)</td>
</tr>
<tr>
<td>Healthy child</td>
<td>205 (80%)</td>
<td>344 (84%)</td>
</tr>
</tbody>
</table>

* p < 0.001

**CASE**

Carrier patient with RPL, ♂ 32 yrs, 46,XX,t(3:19)(q25.1;q13.3) is confused

**IMPACT OF an ABNORMAL GENETIC TEST:**

Does she dare become pregnant again?
What is the psychological impact?
And if pregnant, does she opt for prenatal diagnosis?
DOES SHE DARE BECOME PREGNANT AGAIN? WHAT IS THE PSYCHOLOGICAL IMPACT?

• More carrier couples refrain from further pregnancies when compared to non-carrier couples:

• 31/205 (15%) carrier couples vs 18/316 (6%) non-carrier couples (p<0.001)

• More carrier couples experience significant distress (Impact of Event Scale)

Serious distress in carrier couples after receiving test results

Figure 2 Mean scores on the IES-R for carriers, partners and controls at three and 12 months.

Vansenne PhD thesis 2011, chapter 9

IF PREGNANT DOES SHE OPT FOR PRENATAL DIAGNOSIS?

• 44% (105/239) of carriers (women) did not undergo PND in a single pregnancy

• only 22% (53/239) of carrier couples (women) did undergo PND in all subsequent ongoing pregnancies.

Vansenne Ferti Steril 2009
Effective screening strategy?

- How many couples need to be tested to avoid the birth of 1 affected child?
- In nearly 12,000 tested couples with RPL, the birth of 2 (possibly 3)* children with an unbalanced chromosome pattern was avoided.
- So, we need to test 4,000 - 6,000 couples with RPL to avoid the birth of one affected child (± 0.02% per couple)

*Deduction from Franssen 2005 & 2006

Risk of viable unbalanced translocation in the general population is 0.06%

So, the risk of an affected child ascertained through RPL equals the risk in the general population.

Most of the time spontaneous abortion is a random event and represents the natural selection process. Although a recurrent factor may be present and may cause one or more losses for a given couple such instances are rare.

Parental karyotyping is not routinely recommended in couples with RPL. It could be carried out after individual assessment of risk.

"Consider in case of the previous birth of a child with congenital abnormalities, offspring with unbalanced chromosome abnormalities in the family."
SUMMARY AND KEY MESSAGES

- Routine parental karyotyping is no longer recommended for couples with RPL, based on:
  - a very low chance of chromosomally unbalanced offspring in carriers.
  - the number of children with congenital malformations in carriers equals the number of children with congenital malformations in non-carriers
  - Parental karyotyping is not without harm, more carrier couples
    - refrain from further children
    - suffer from distress

Counselling and reassurance are essential

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REBUTTAL

Karyotyping for RPL- con rebuttal Goddijn

NO!
LBR after NAT CONCEPTION vs PGD

- Meta-analysis was precluded owing to significant heterogeneity between studies
- A pooled total of 847 couples who conceived naturally had a LBR ranging from 25–71%
- A pooled total of 562 couples who underwent IVF and PGD had a LBR ranging from 26.7–87%

PGD for carrier couples and RPL?

NO!

- Natural compared The question is redundant if you do not karyotype
- The carrier The question is redundant if you do not karyotype.
- The question is redundant if you do not karyotype.

State of the art work-up RPL

<table>
<thead>
<tr>
<th>Clinical problem</th>
<th>Tests</th>
<th>Findings</th>
<th>Health care (evaluation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent Pregnancy Loss ≥ 2 losses</td>
<td></td>
<td></td>
<td>De-implement parental karyotyping</td>
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<td></td>
<td></td>
<td></td>
<td>Anticoagulant</td>
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<td></td>
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<td></td>
<td>AUFJE-2 (RCT)</td>
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<td></td>
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<td></td>
<td>Supportive care</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>TOLST (RCT)</td>
</tr>
</tbody>
</table>
HOW DO WE KNOW IF A DIAGNOSTIC TEST IS EFFECTIVE?

**Pathophysiological reasoning**

- Reindollar: N = 1 couple no reproductive outcome
  - Where are the other 11,999 couples?

**Epidemiological evidence**

- Goddijn: N=12,000 couples Reproductive outcome in carriers and a subset of non-carriers.

FINAL SLIDE

Parental karyotyping is not routinely recommended in couples with RPL

- Please adopt the ESHRE RPL guideline 2017 & adapt your local protocol
## LBR in carrier couples (natural conception)

<table>
<thead>
<tr>
<th>Author</th>
<th>Design</th>
<th>Study period</th>
<th>Miscarriage rate</th>
<th>Live birth rate (male %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rubino et al., 2017</td>
<td>Case-control</td>
<td>1996-2001</td>
<td>NA</td>
<td>56.36</td>
</tr>
<tr>
<td>Depay et al., 2014</td>
<td>Case-control</td>
<td>2007-2011</td>
<td>50</td>
<td>41</td>
</tr>
<tr>
<td>Fries et al., 2014</td>
<td>Case-control</td>
<td>1992-2011</td>
<td>114.40</td>
<td>44.30</td>
</tr>
<tr>
<td>Kehl-Kirchhoff et al., 2013</td>
<td>Prospective cohort</td>
<td>2006-2009</td>
<td>24.40</td>
<td>47</td>
</tr>
<tr>
<td>Drudi and Stefancovic, 2012</td>
<td>Prospective cohort</td>
<td>2006-2011</td>
<td>38</td>
<td>55</td>
</tr>
<tr>
<td>Pal et al., 2009</td>
<td>Prospective cohort</td>
<td>2005-2006</td>
<td>58</td>
<td>5%</td>
</tr>
<tr>
<td>Sepulcre-Rojan et al., 2008</td>
<td>Prospective cohort</td>
<td>2002-2005</td>
<td>27</td>
<td>45</td>
</tr>
<tr>
<td>Stephens and Garcia, 2006</td>
<td>Prospective cohort</td>
<td>1992-2006</td>
<td>28</td>
<td>75</td>
</tr>
<tr>
<td>Francisco et al., 2004</td>
<td>Case-control</td>
<td>1992-2000</td>
<td>48</td>
<td>49</td>
</tr>
<tr>
<td>Cam et al., 2004</td>
<td>Retrospective cohort</td>
<td>1996-2001</td>
<td>54.80</td>
<td>45</td>
</tr>
</tbody>
</table>