How can we reduce the preterm delivery rate?

Bo Jacobsson

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10 Congrés Català d'Obstetrícia i Ginecologia

7, 8, 9 novembre de 2018
Auditori AXA, Barcelona

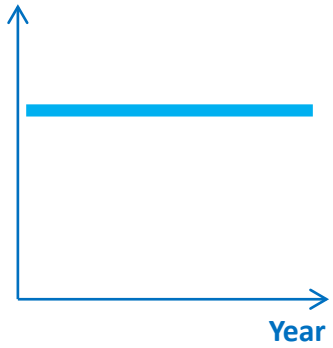
CONFLICTS OF INTEREST

Performed NIPT clinical diagnostic trails for Ariosa, Natera and Vanadis –
NO personal reimbursements, no talks or promotional actives for the companies

Performed an intra-amniotic infection clinical diagnostic trail for Hologic –
NO personal reimbursements, no talks or other promotional activities for the company

Pregnancy

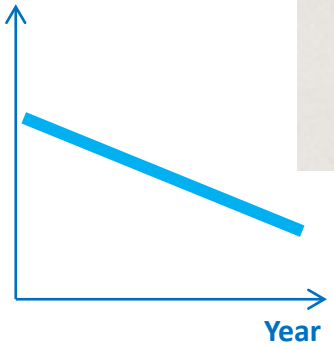
Preterm delivery rate



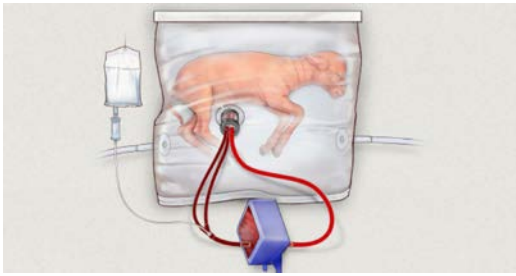
Little progress

Neonatal period

Neonatal mortality

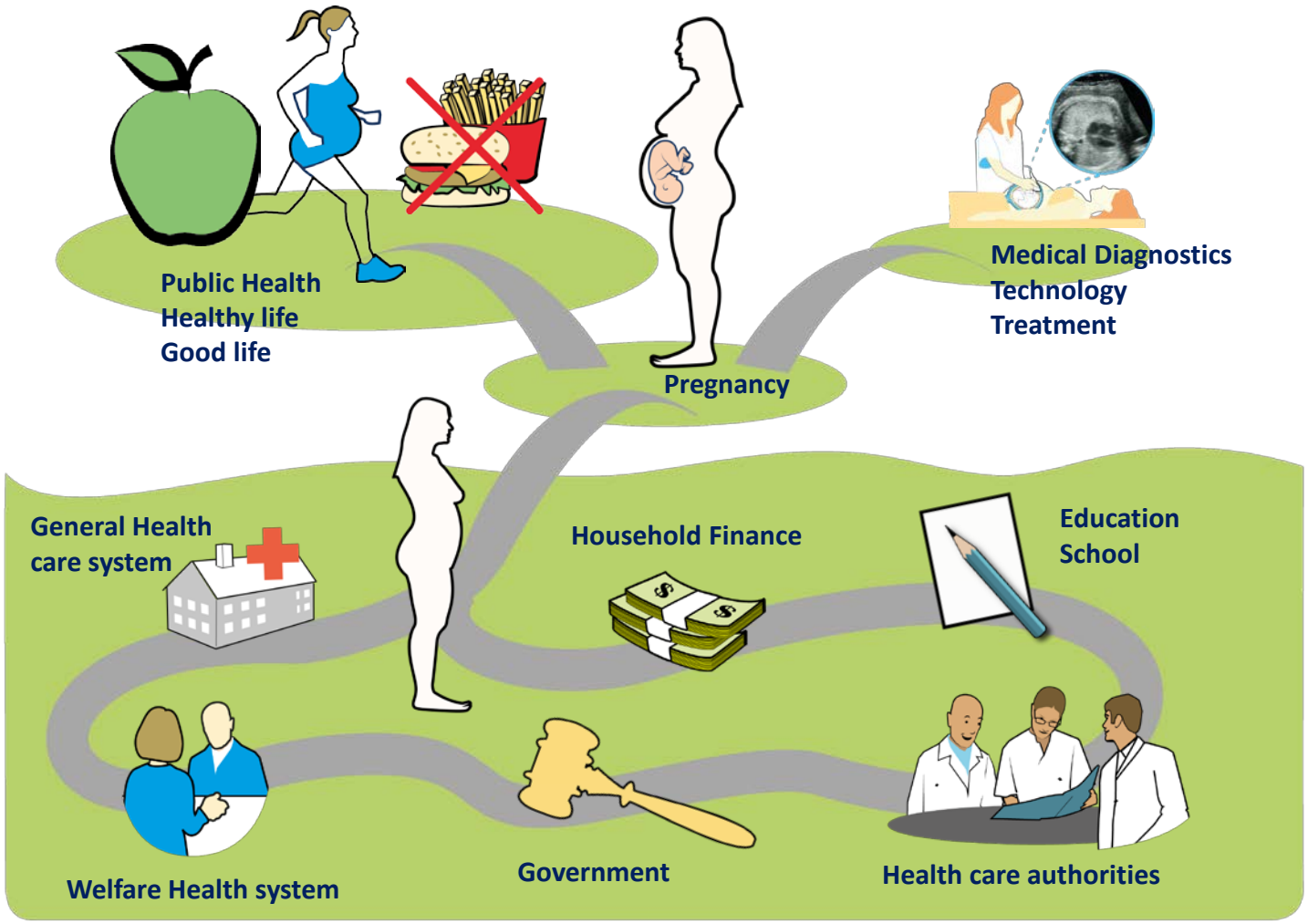


Huge progress

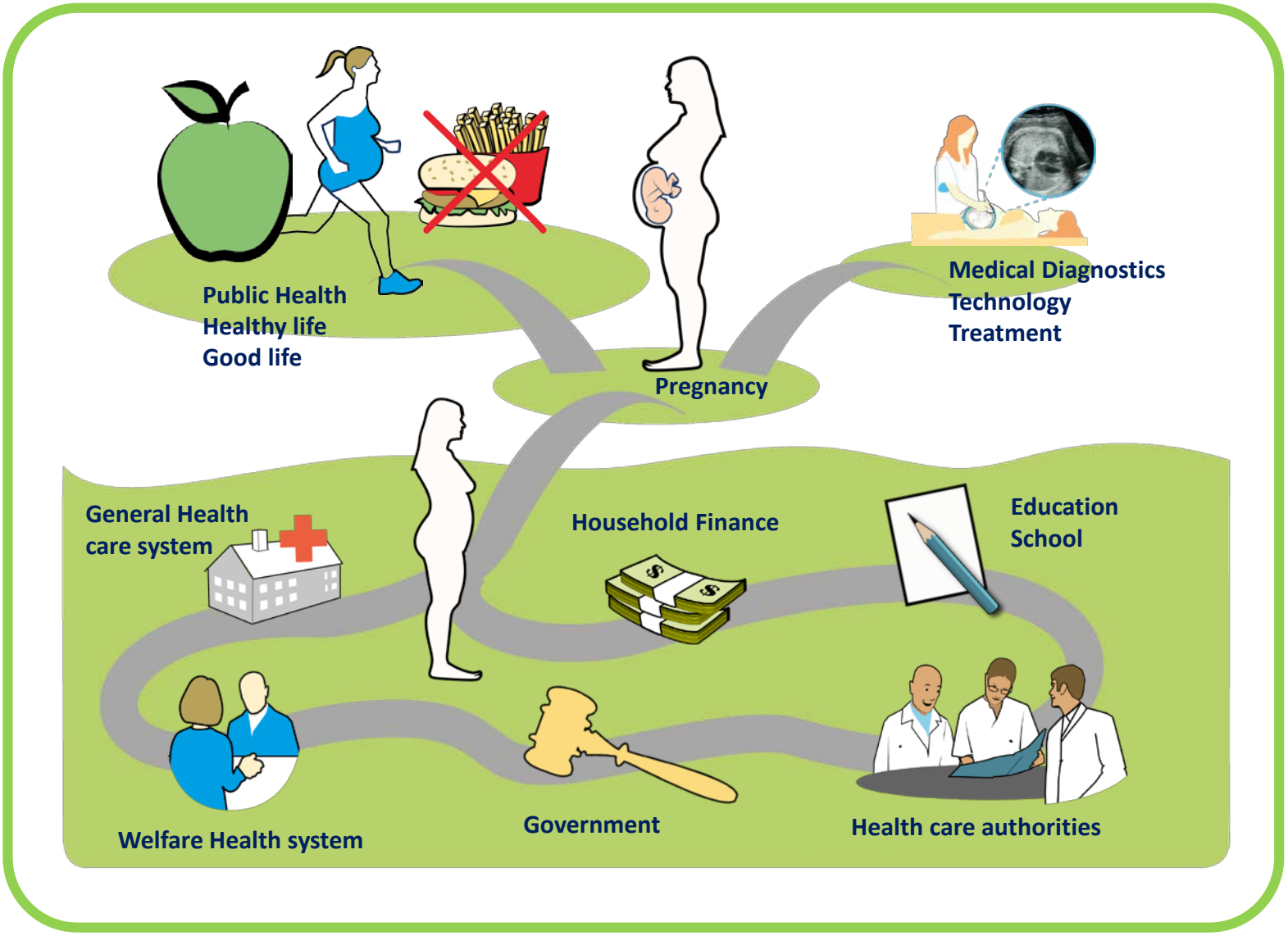


Due to lack of basic understanding of pregnancy and delivery
Major research effort to understand this pregnancy issues

A huge international effort on women´s health

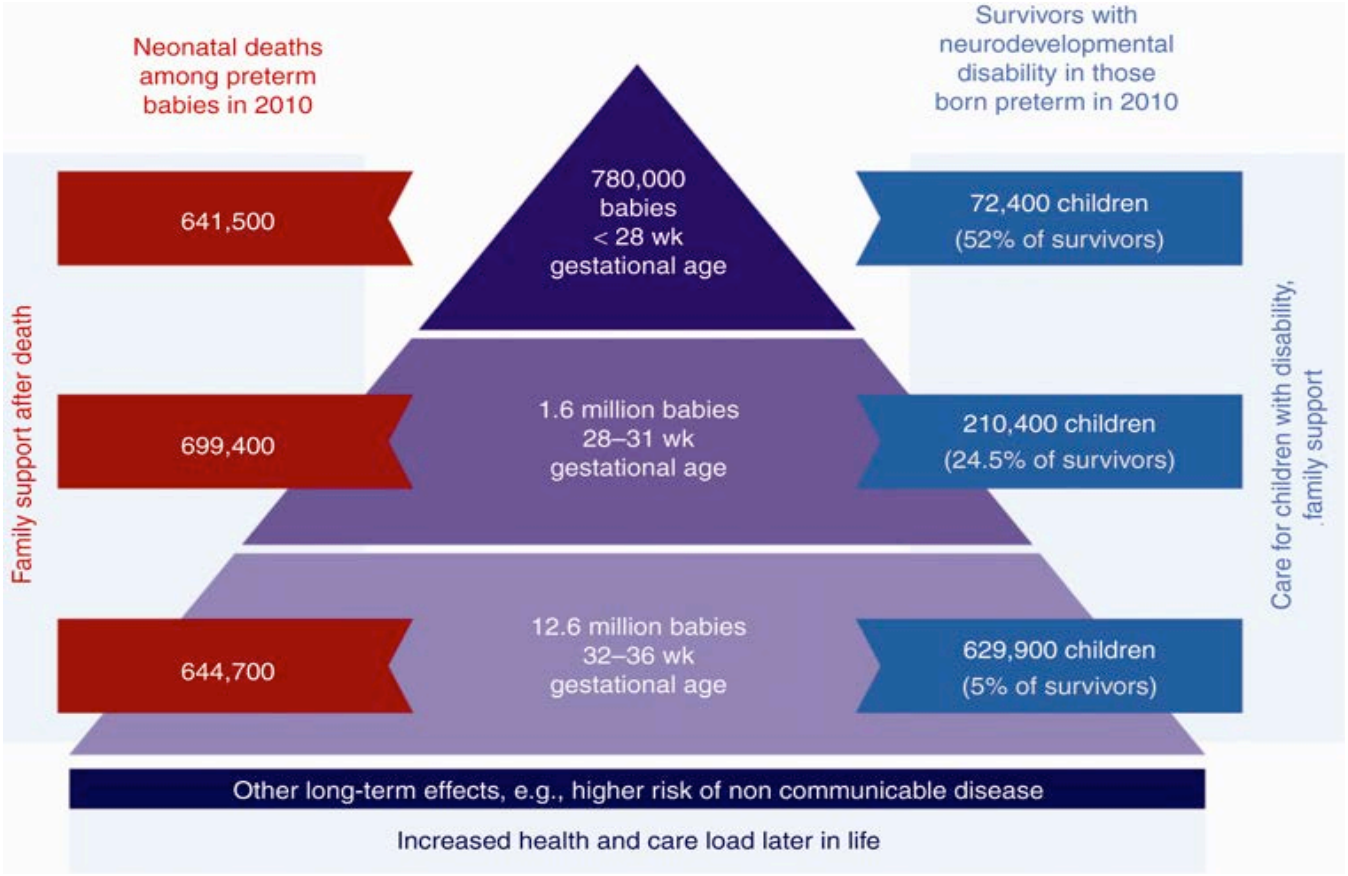


Research and constant simultaneous registration and validation



Mandatory registers – continuous validation of data and interventions

Burden of mortality and impairment for 15 million preterm babies born in 2010



Blencowe H et al 2013 Pediatric Research 74:

Shift some of the focus from only early to some of the late

OVERVIEW OF THE TALK

1. PRETERM DELIVERY RATES? SO WHERE IS THE BOTTOM LINE? BIOLOGICAL VARIATIONS?

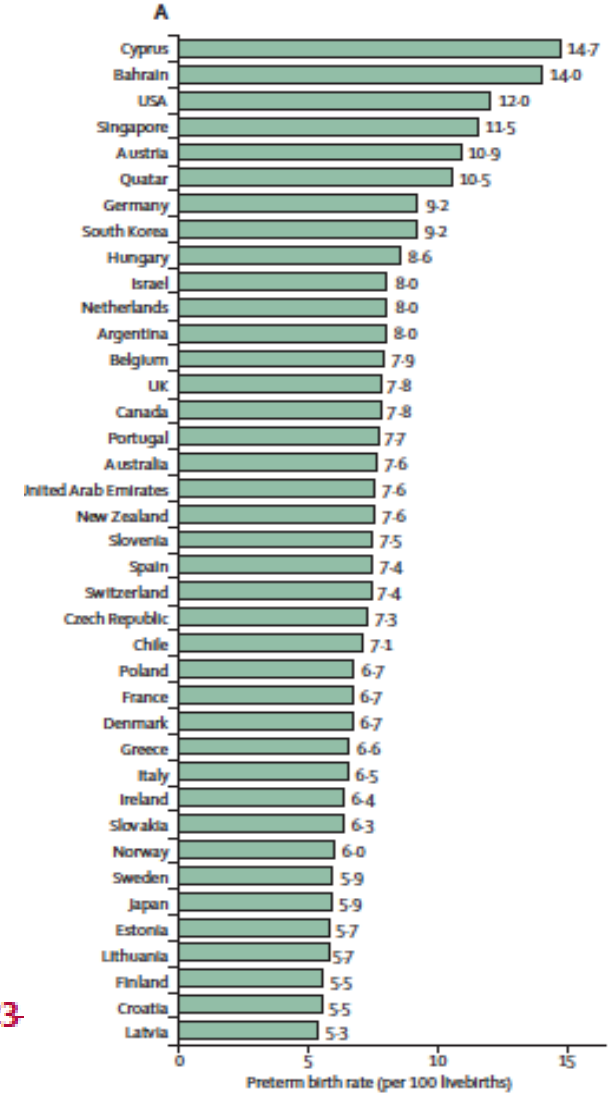
2. REFLEXION ON PHENOTYPE – WHAT CAN BE EXPECTED?

3. CALCULATION EXEMPLES FROM CURRENT KNOWLEDGE?

4. WHICH STRATGIES WILL BE NEEDED? STRATEGIES ON MANY DIFFERENT FRONTS.

Preventing preterm births: analysis of trends and potential reductions with interventions in 39 countries with very high human development index

Hannah H Chang, Jim Larson, Hannah Blencowe, Catherine Y Spong, Christopher P Howson, Sarah Cairns-Smith, Eve M Lackritz, Shoo K Lee, Elizabeth Mason, Andrew C Serazin, Salimah Walani, Joe Leigh Simpson, Joy E Lawn, on behalf of the Born Too Soon preterm prevention analysis group



Lancet 2013; 381: 223

HUGE VARIATION OF PRETERM DELIVERY RATES IN HIGH INCOME COUNTRIES

CYPRES 14.7%
GERMANY 9.2%
…..
FINLAND 5.5%
CROATIA 5.5%
LATVIA 5.3%

Original investigation

The Distribution of Clinical Phenotypes of Preterm Birth Syndrome Implication for Prevention

Intergrowth – 21st Project

Low risk population PRETERM BIRTH RATE 4.5%

Jama Pediatrics. 2015;169(3);220-229

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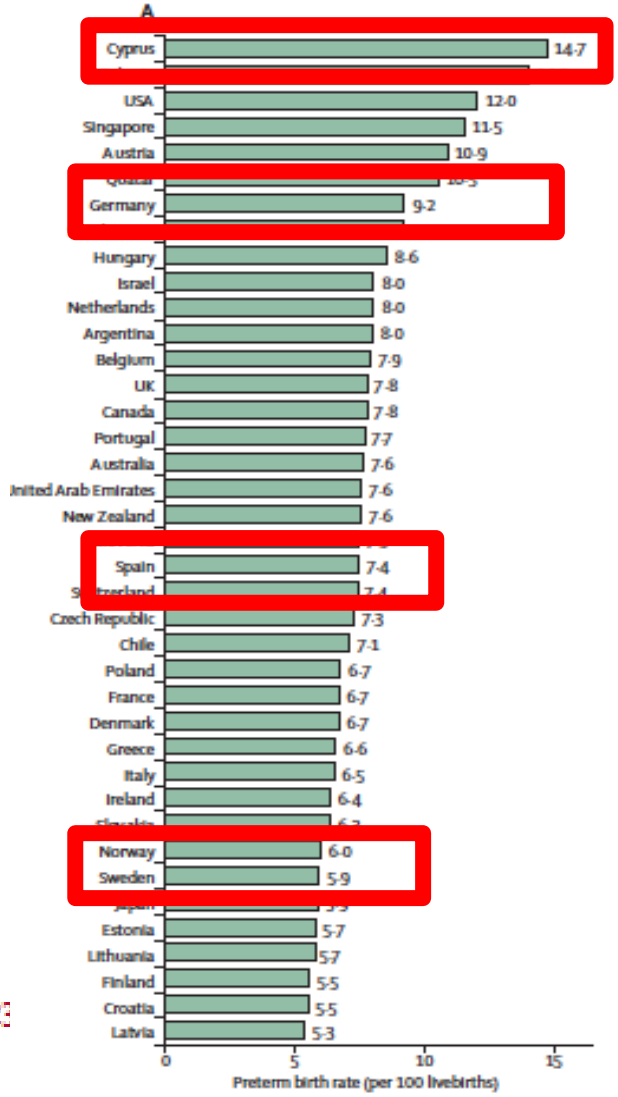
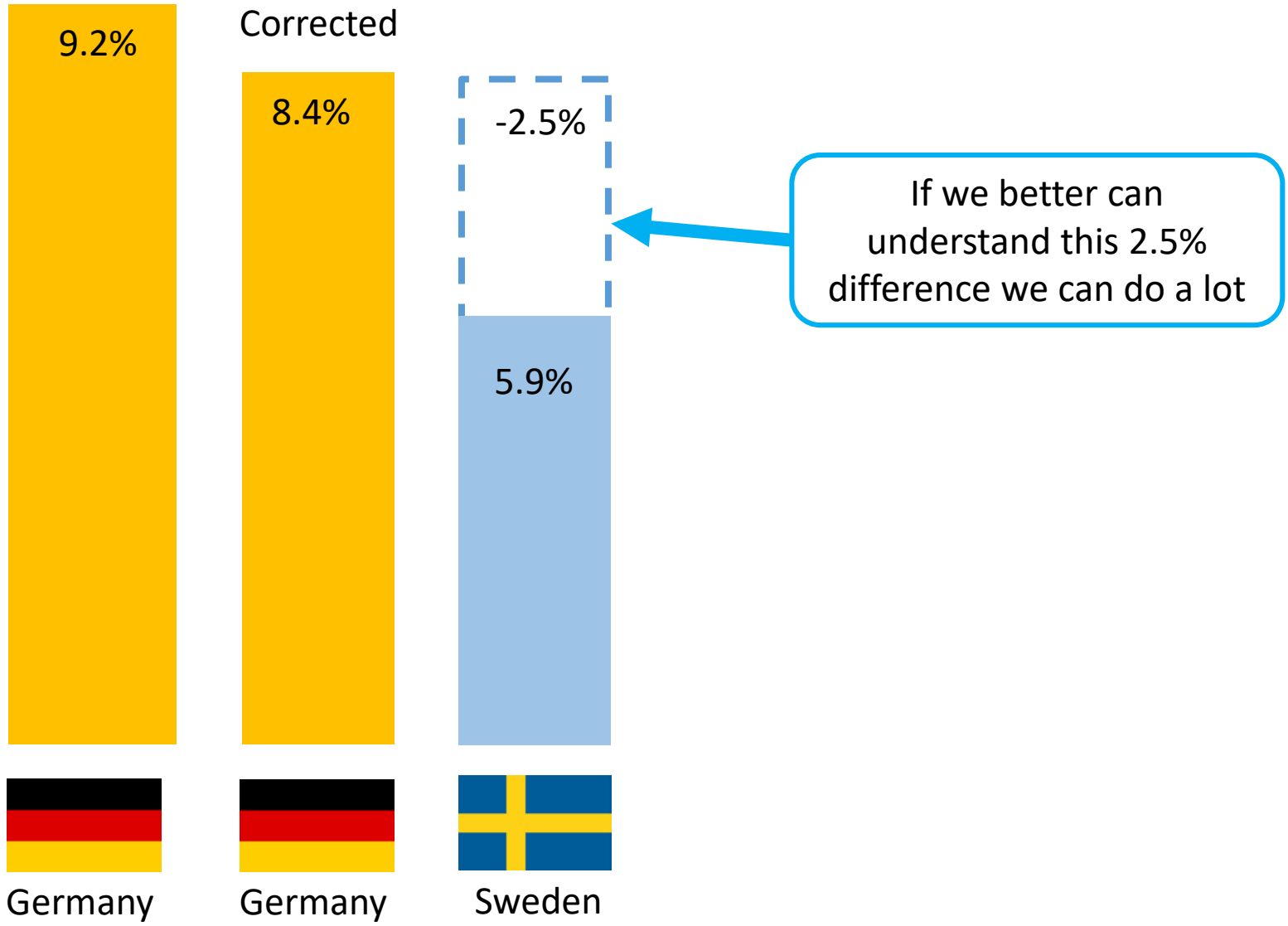


Lancet 2013; 381: 223

I think we can agree on these huge differences are most likely not due to biology!


9.2%
Corrected
8.4%
-2.5%
5.9%
If we better can understand this 2.5% difference we can do a lot
Germany
Germany
Sweden

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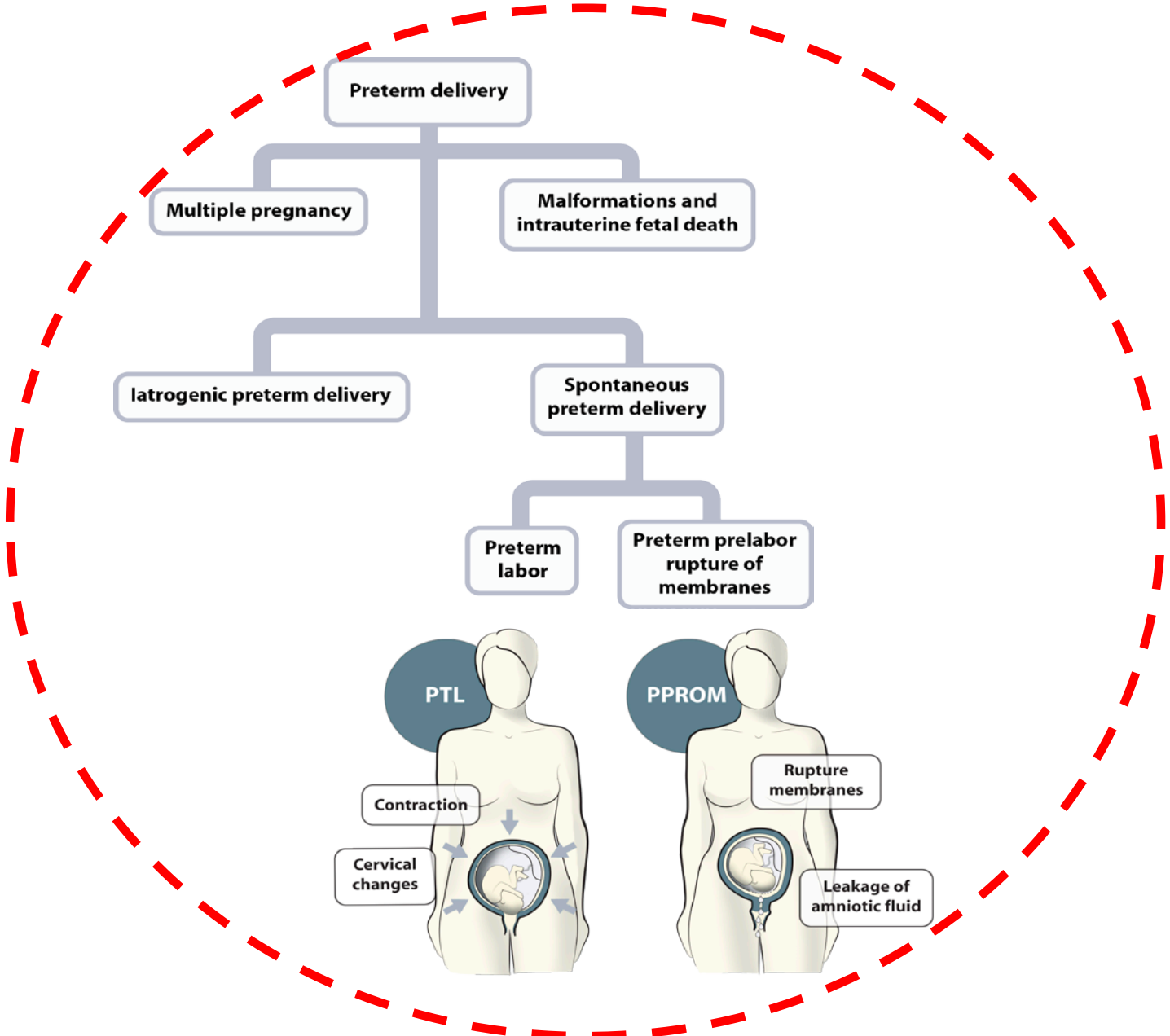
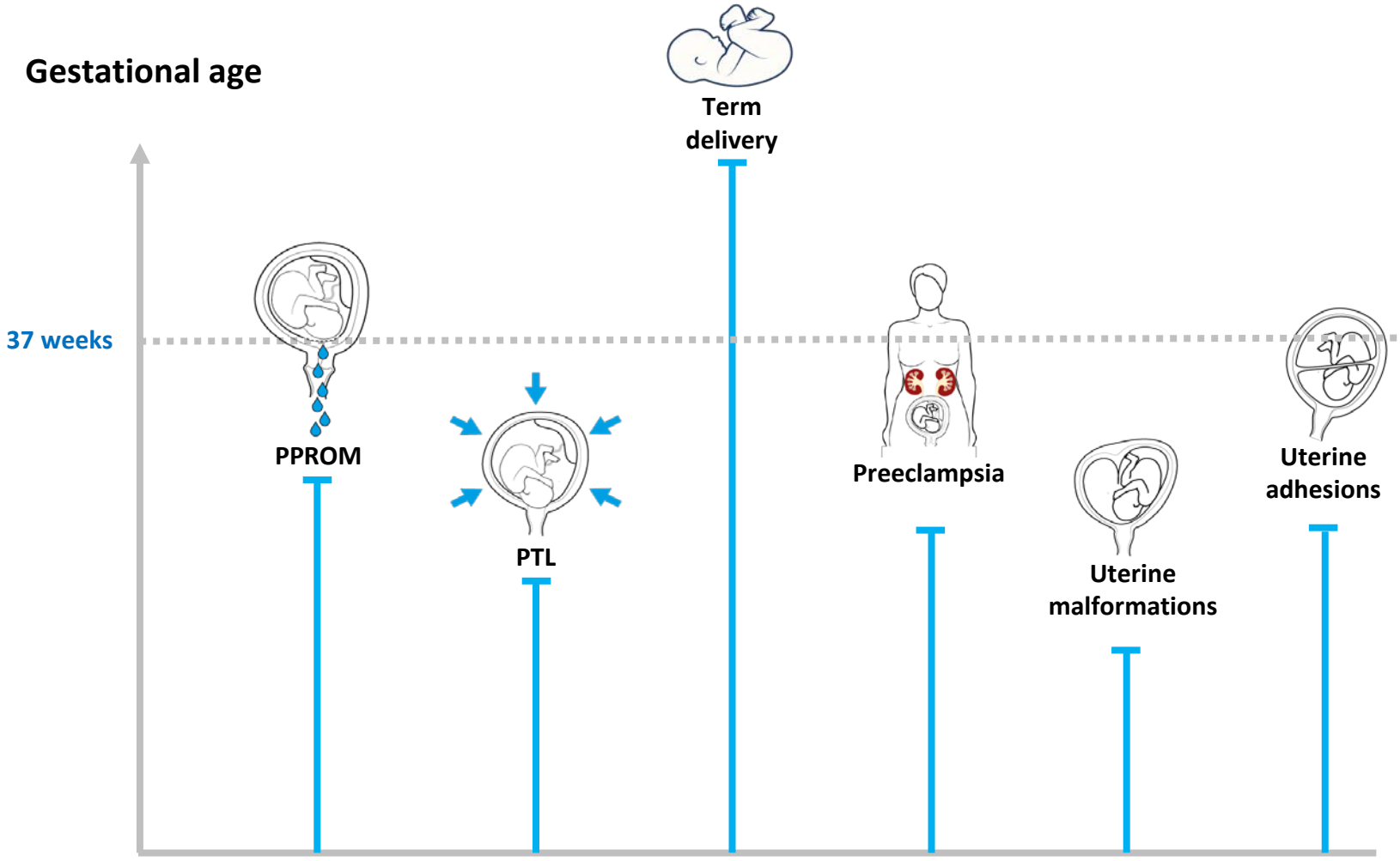
Preterm delivery

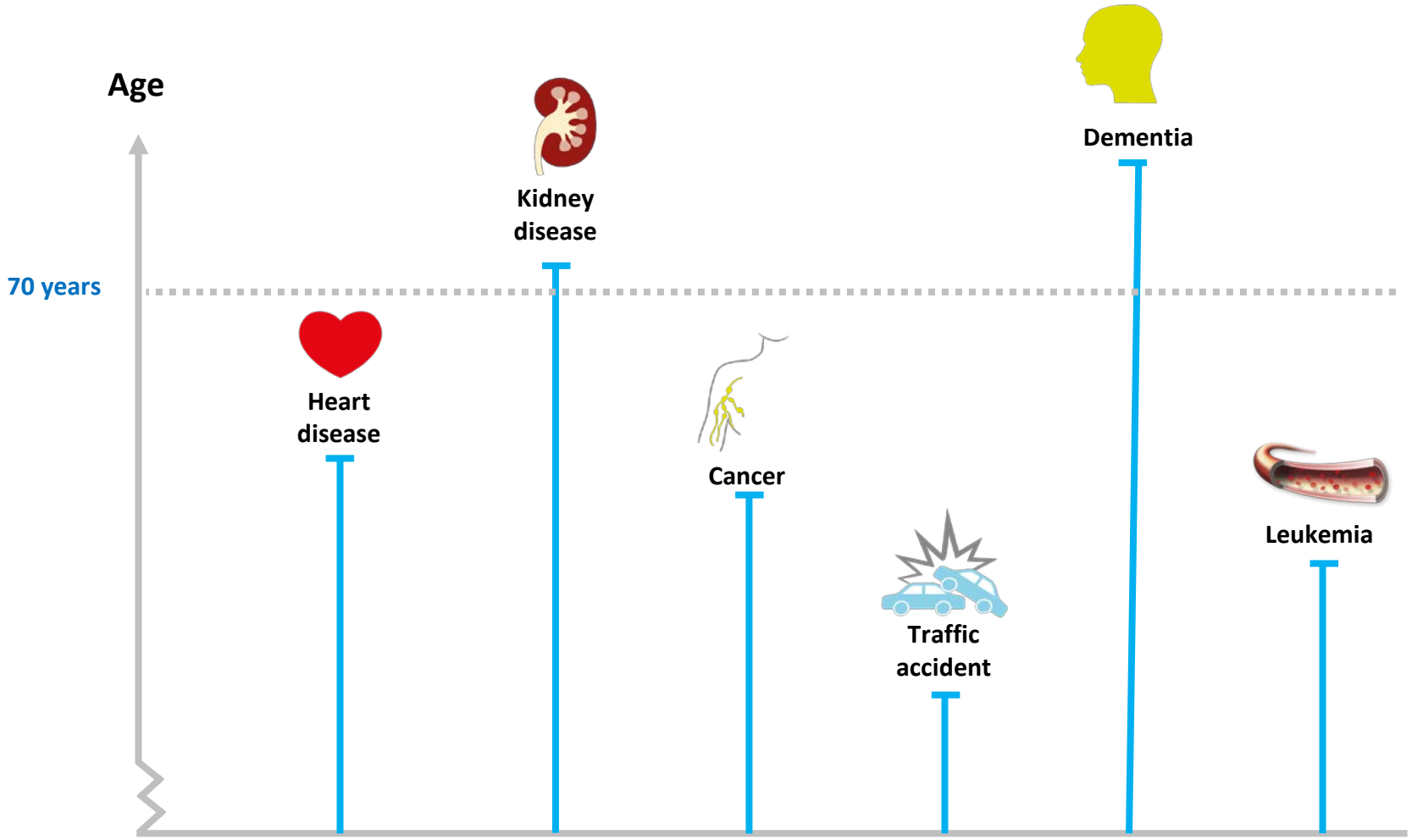


Preterm delivery

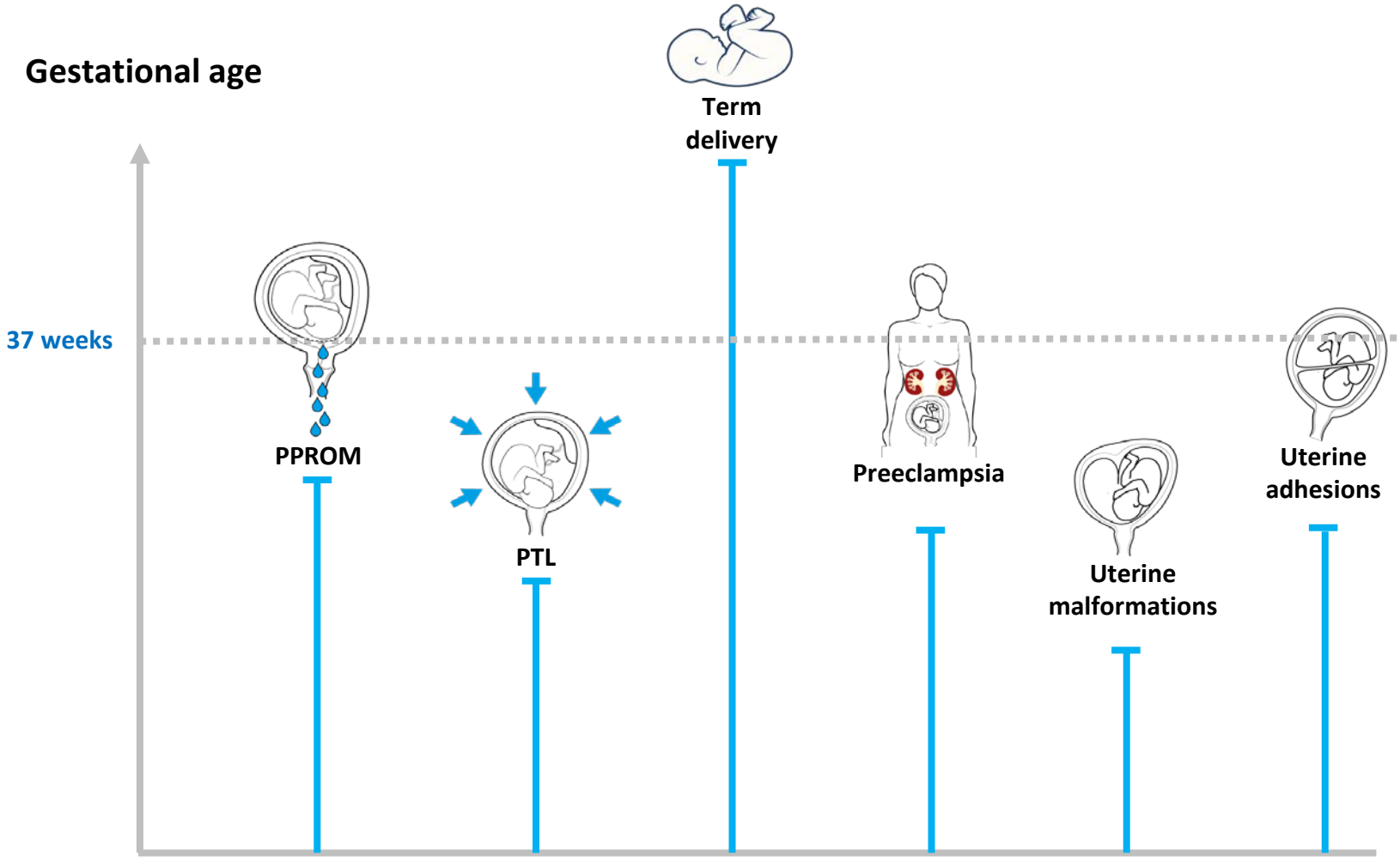
Preterm delivery – syndrome of syndromes



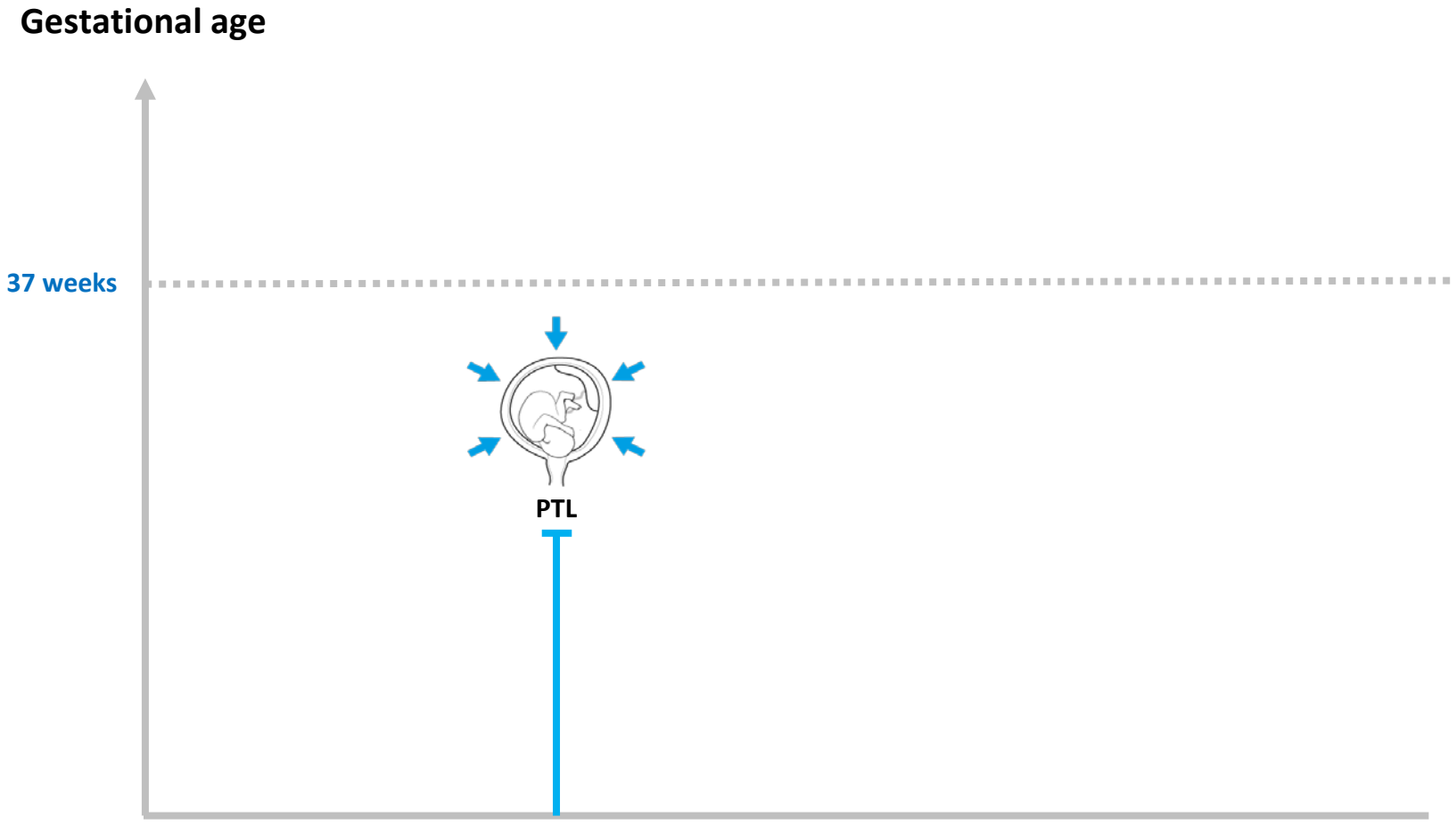
Mortality < 70 years



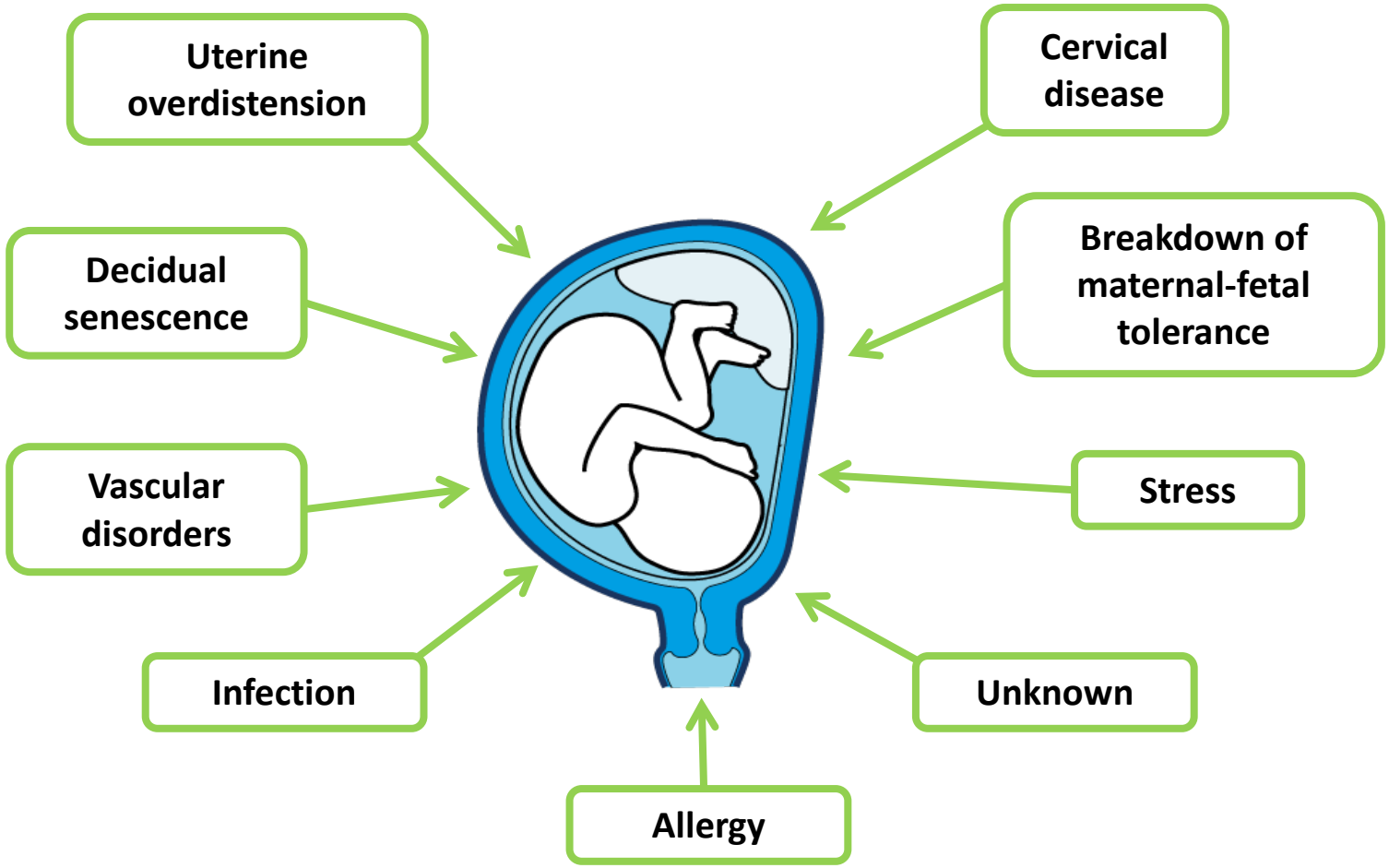
Preterm delivery – syndrome of syndromes



Preterm labor

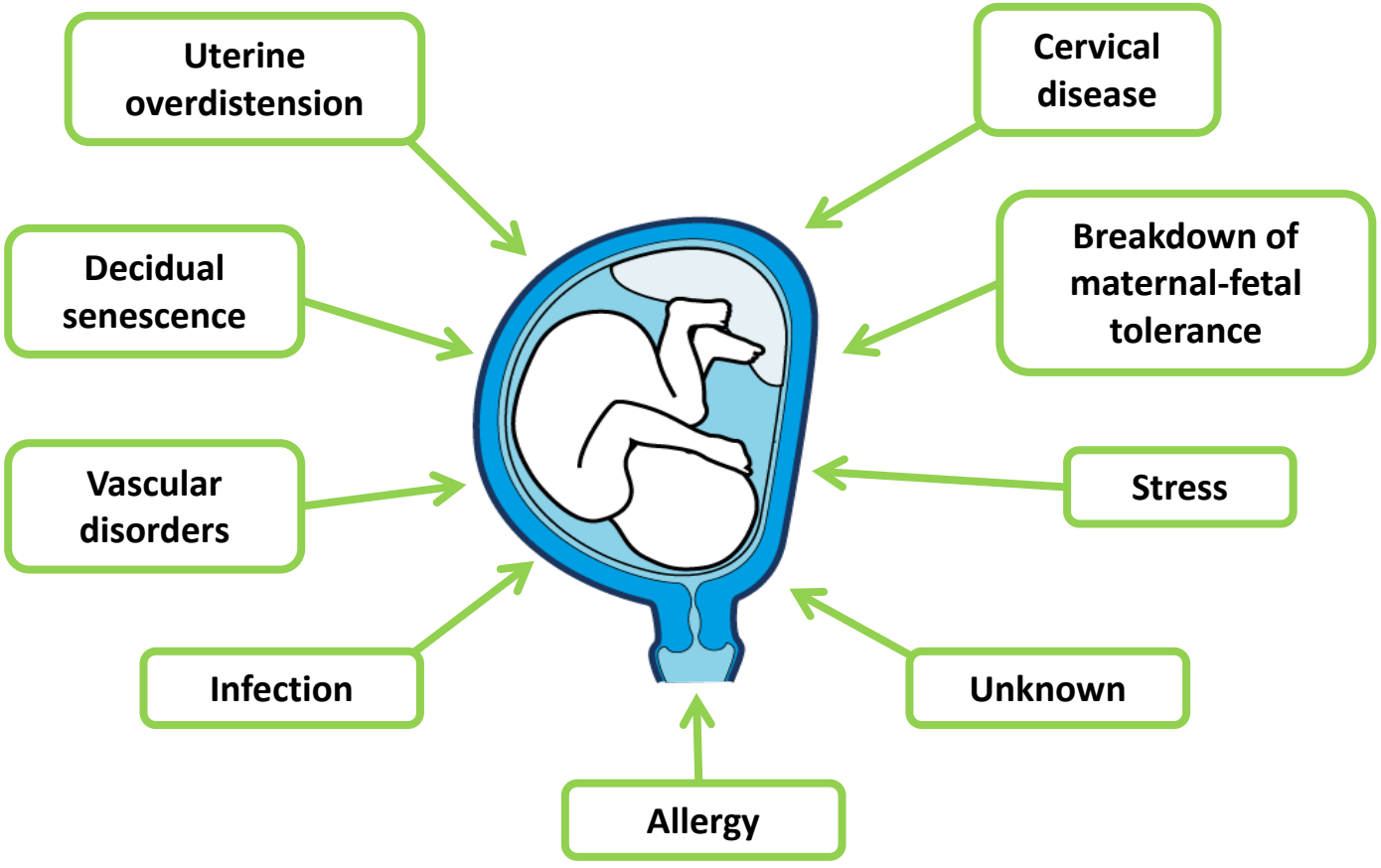


Preterm labor



Romero Science 2014

CONCLUSION: NO EASY UNDERSTANDING OF A PHENOTYPE LIKE THIS – SYNDROME OF SYNDROMES



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HOWEVER: NOT A DEAD END

USE CONTINIOUS PHENOTYPE FOR BETTER BIOLOGICAL UNDERSTANDING

THE FINAL BREAKTHROUGH

The NEW ENGLAND JOURNAL of MEDICINE

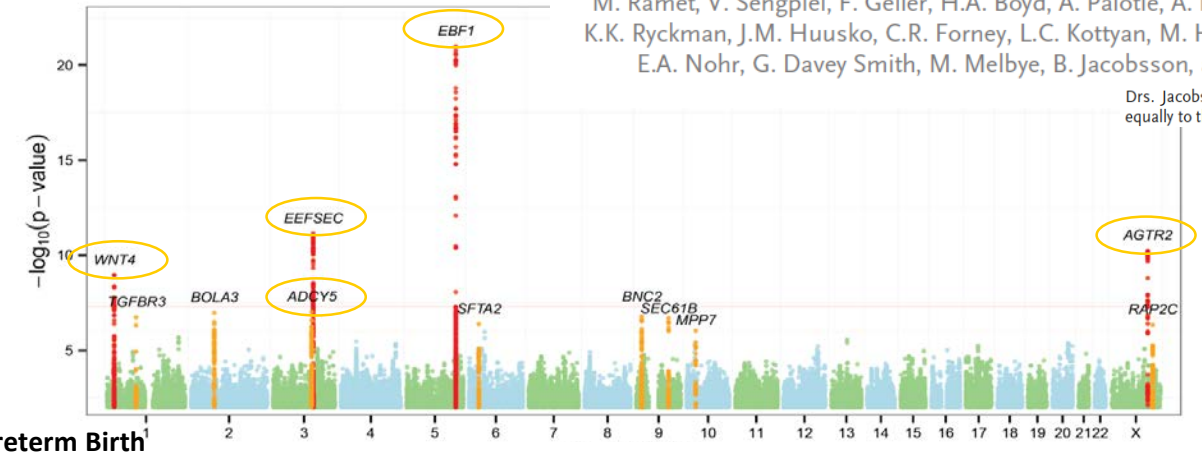
ORIGINAL ARTICLE

Genetic Associations with Gestational Duration and Spontaneous Preterm Birth

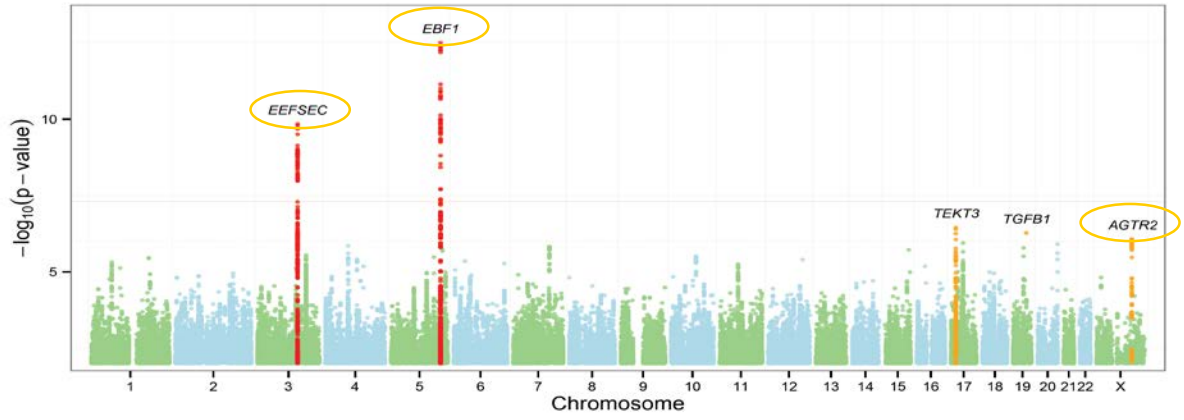
G. Zhang, B. Feenstra, J. Bacelis, X. Liu, L.M. Muglia, J. Juodakis, D.E. Miller, N. Litterman, P.-P. Jiang, L. Russell, D.A. Hinds, Y. Hu, M.T. Weirauch, X. Chen, A.R. Chavan, G.P. Wagner, M. Pavličev, M.C. Nnamani, J. Maziarz, M.K. Karjalainen, M. Rämet, V. Sengpiel, F. Geller, H.A. Boyd, A. Palotie, A. Momany, B. Bedell, K.K. Ryckman, J.M. Huusko, C.R. Forney, L.C. Kottyan, M. Hallman, K. Teramo, E.A. Nohr, G. Davey Smith, M. Melbye, B. Jacobsson, and L.J. Muglia

Drs. Jacobsson and Muglia contributed equally to this article.

Gestational Duration



Preterm Birth



N Engl . *1156-67*
DOI: 10.1056/NEJMoal1612665

Genotypes of 44,000 women in collaboration with 23andMe, Inc.

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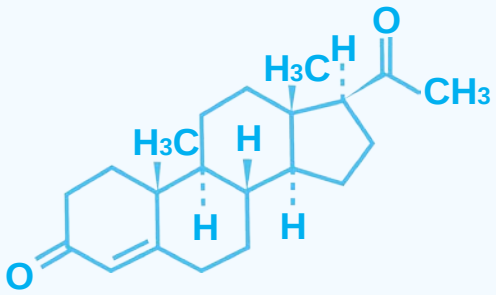
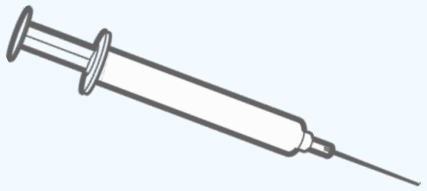
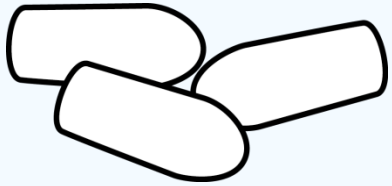
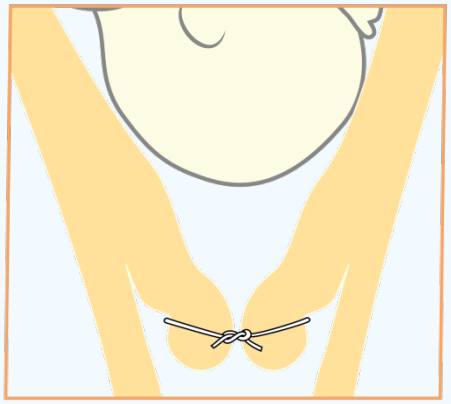
Progesteron

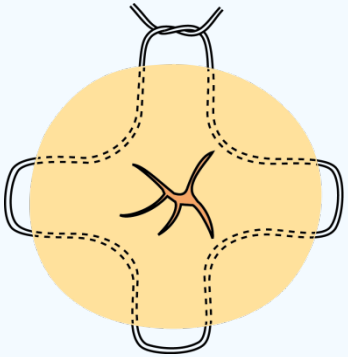




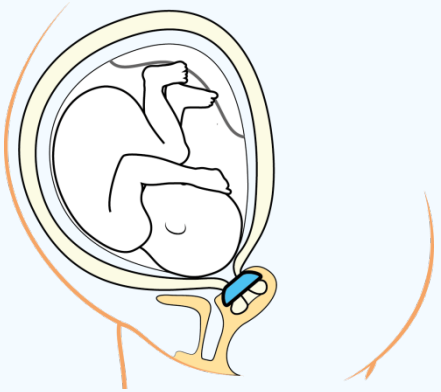


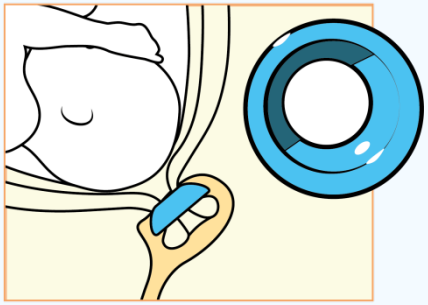
Cervical cerclage





Cervical pessary





OR around 0.6 but how much do that mean in real figures on the preterm delivery rate?

The effect of the treatment

X

The fraction of the overall phenotype related to the specific indications for the treatment

=

Reduction of the overall phenotype rate

Population Attributable Fraction

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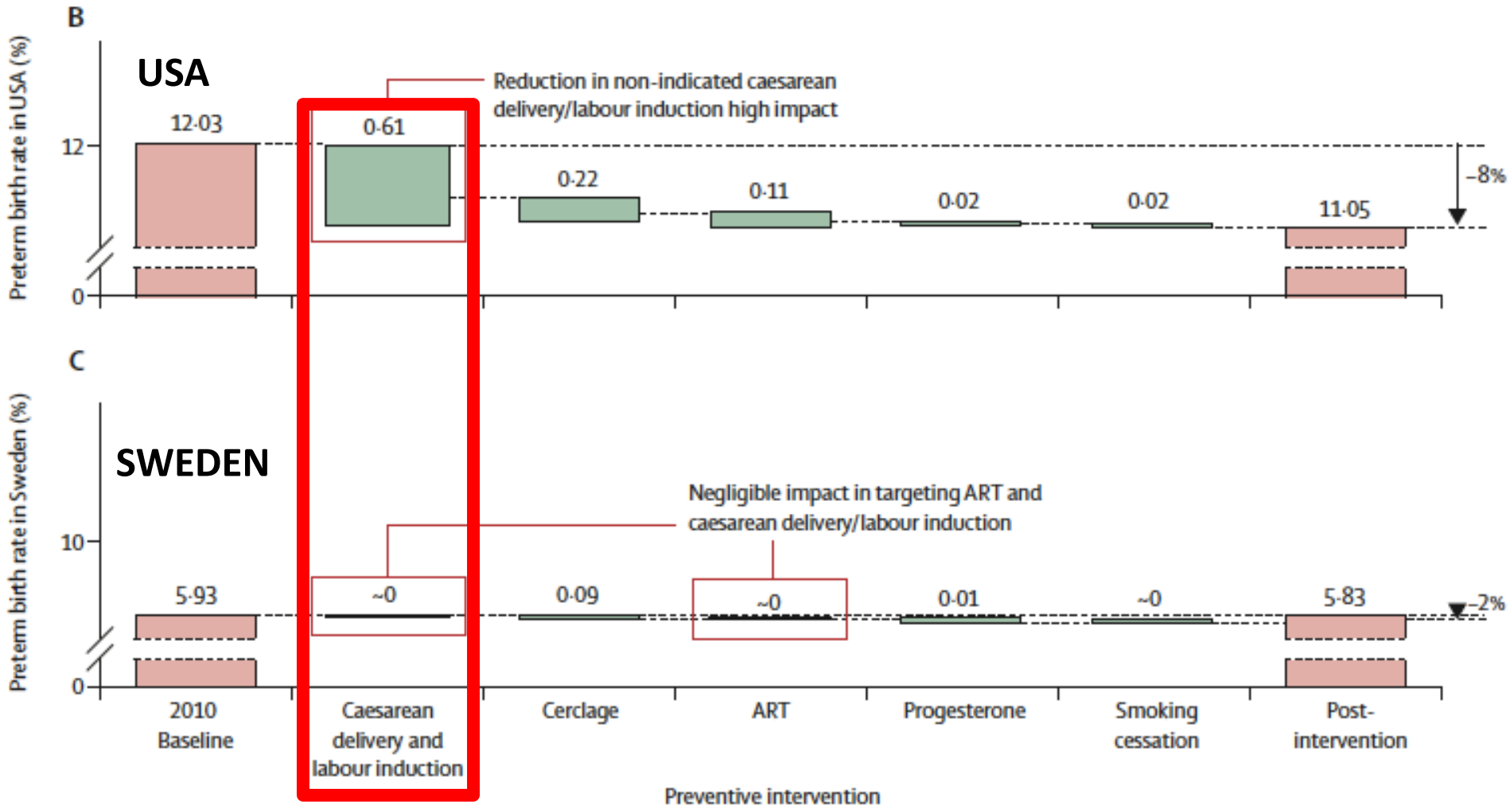
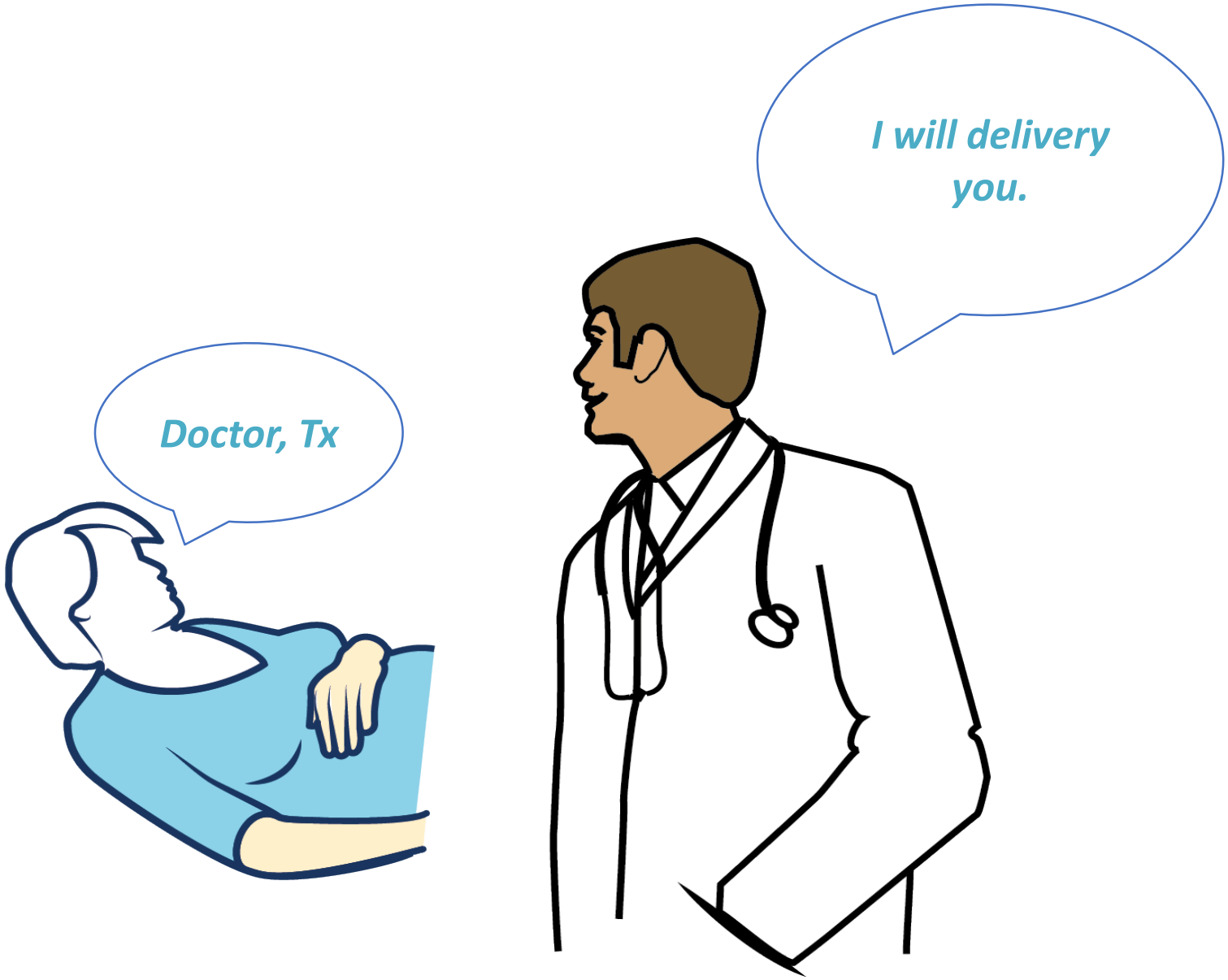
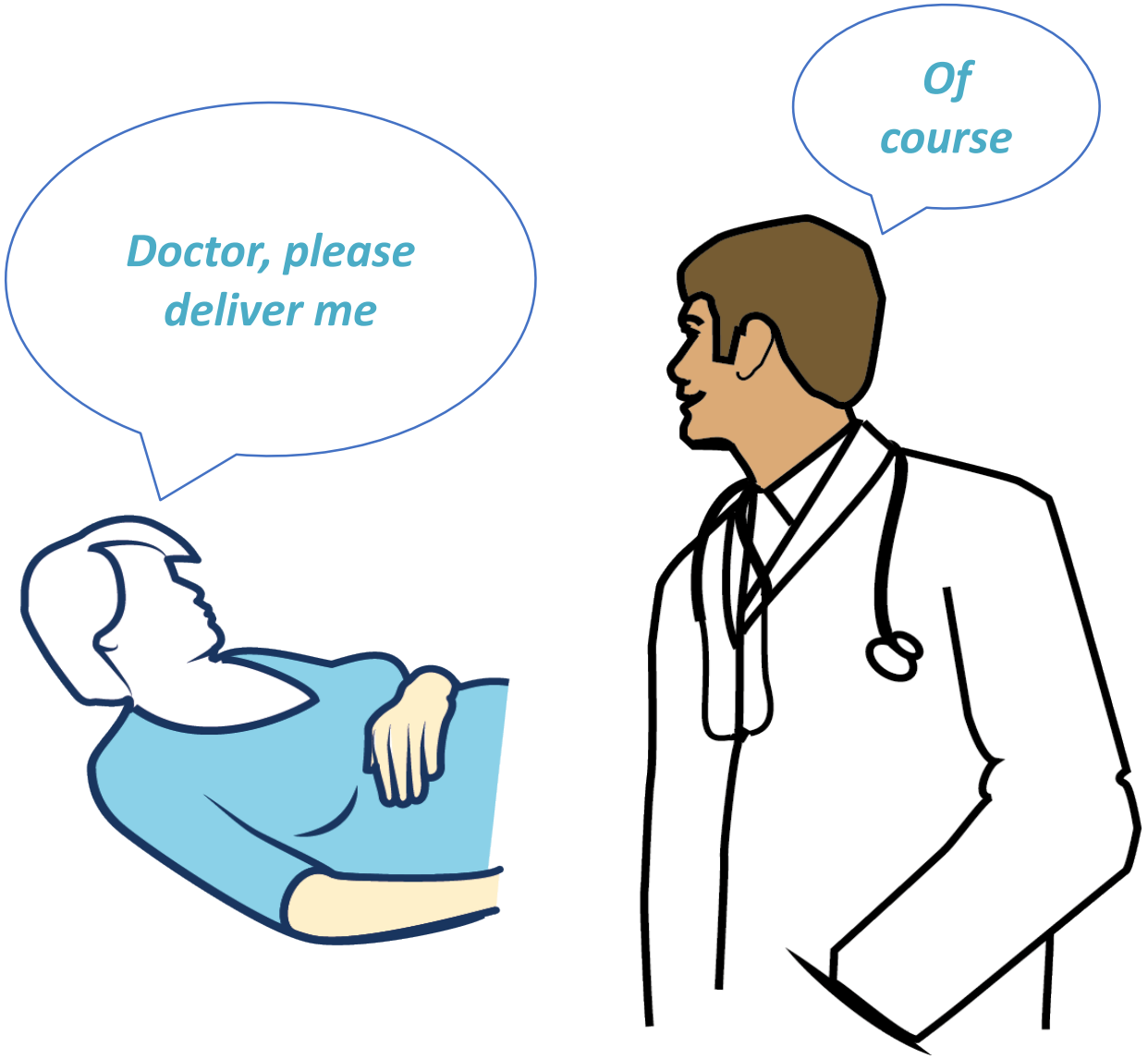


Figure 6: **Projected change from 2010 baseline preterm birth rate showing modelled contribution of the five selected interventions**

Many doctors want action

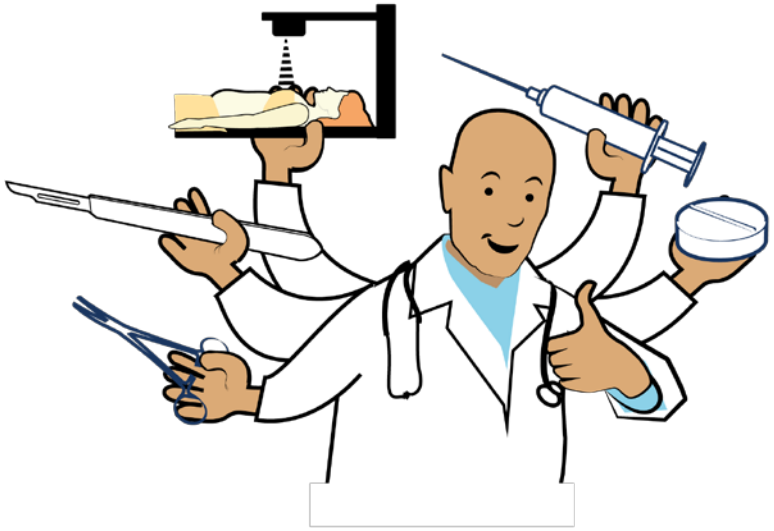


Many patients want action



Many doctors want to do things

We need to produce and follow guidelines



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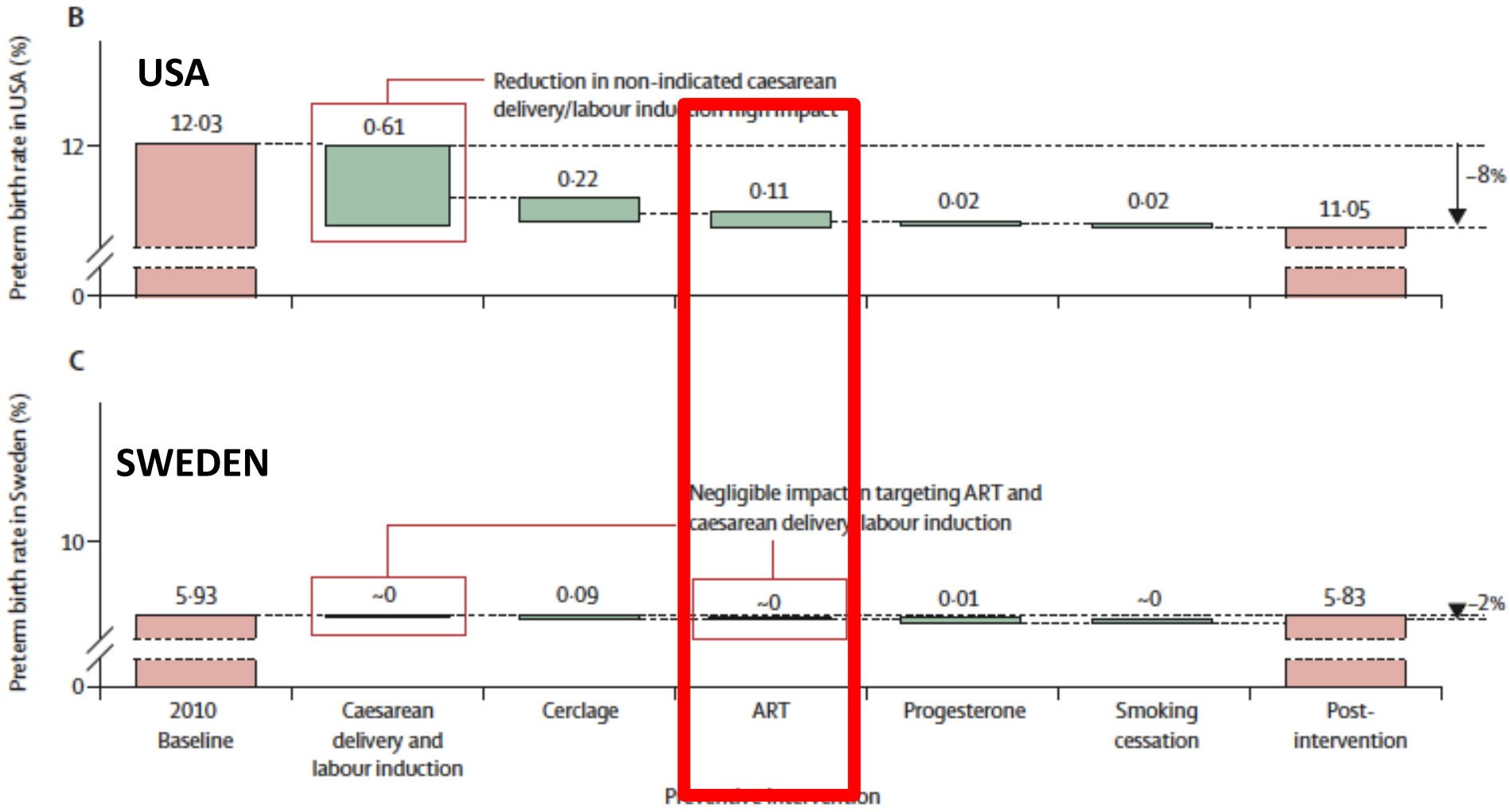

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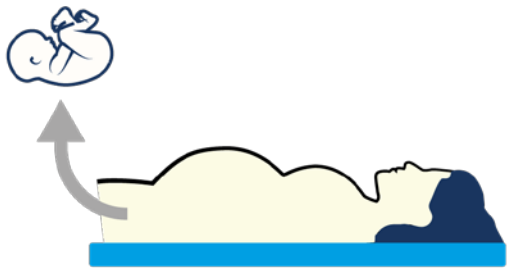
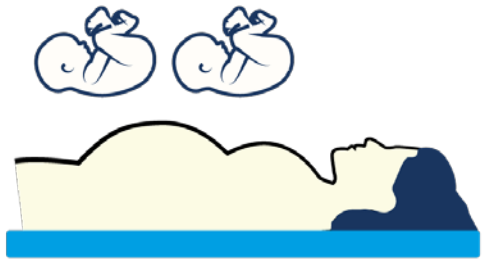
What is the best outcome of the fertility treatment?

One healthy baby

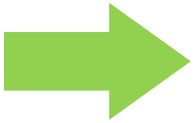
Multiple pregnancy is a problem both from ovarian stimulation and from multiple embryo transfer



≥ Week 37 or ≥ 39

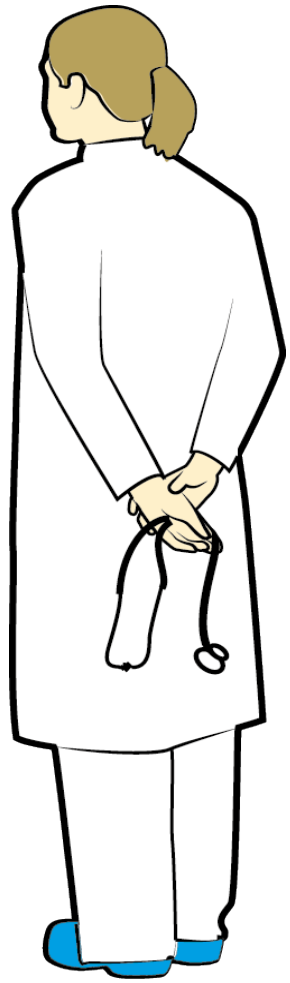


ART



Gestational age and multiple pregnancy matters

First: do no harm



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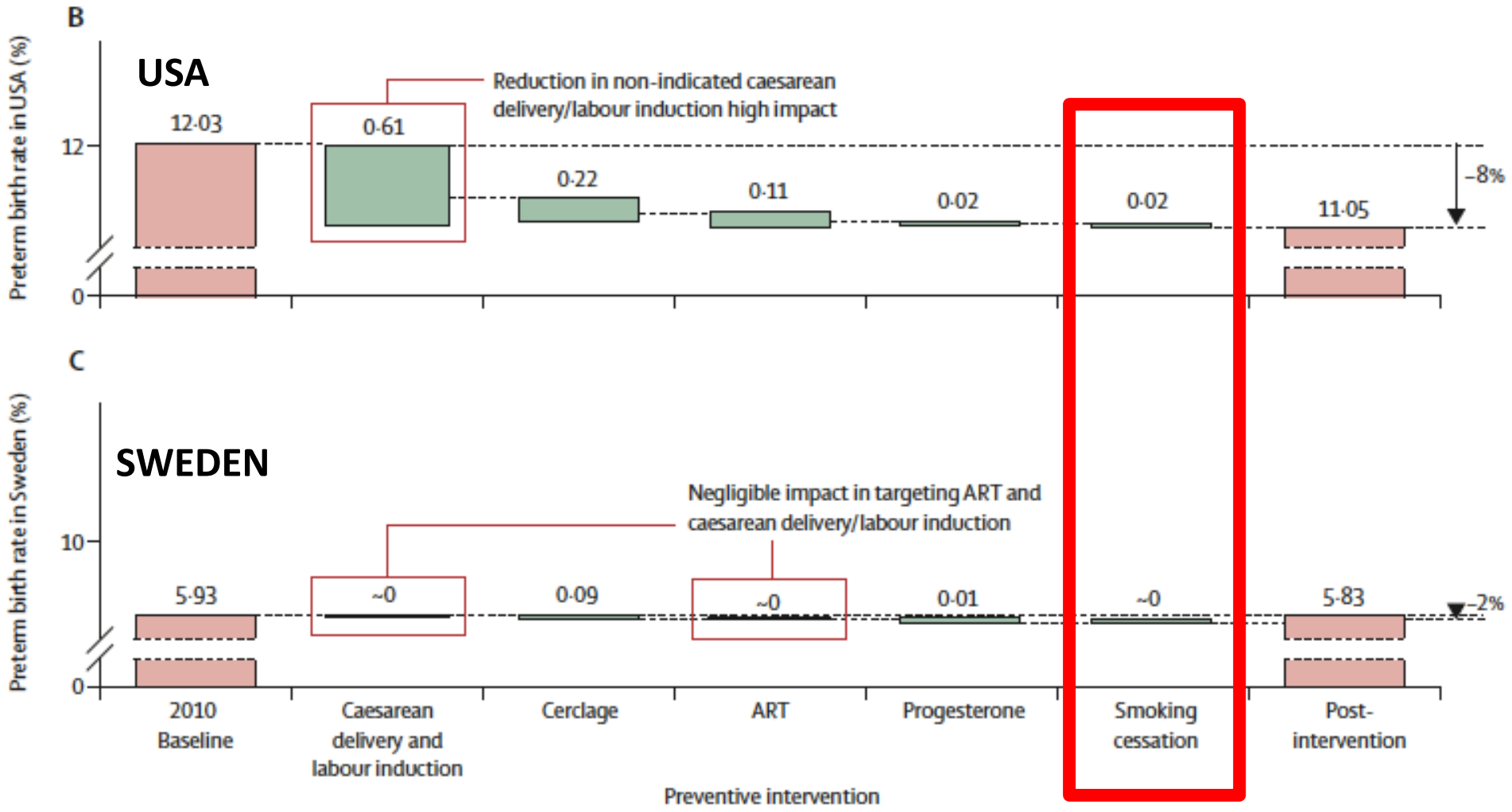

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Lancet 2013; 381: 223–34

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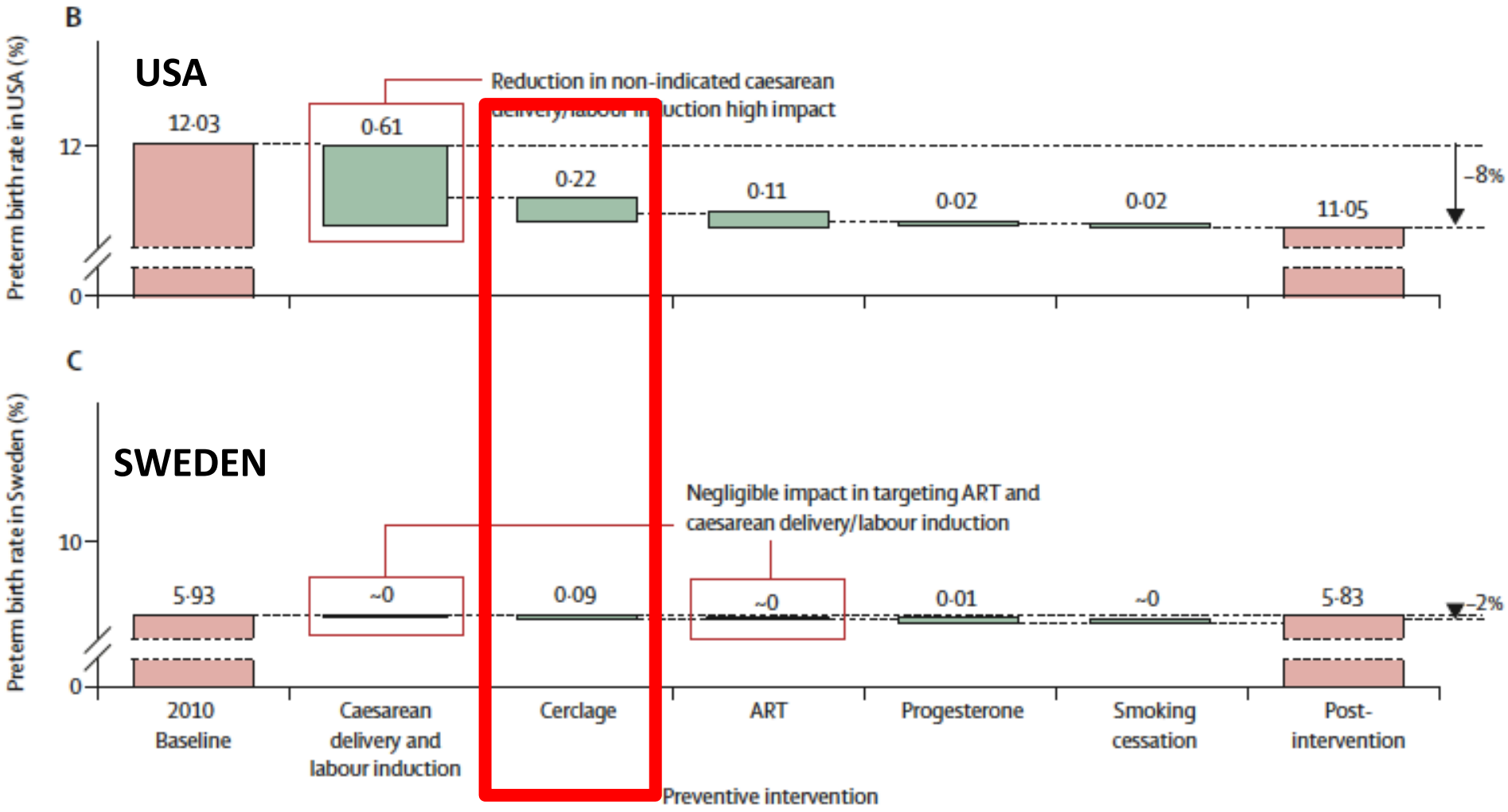

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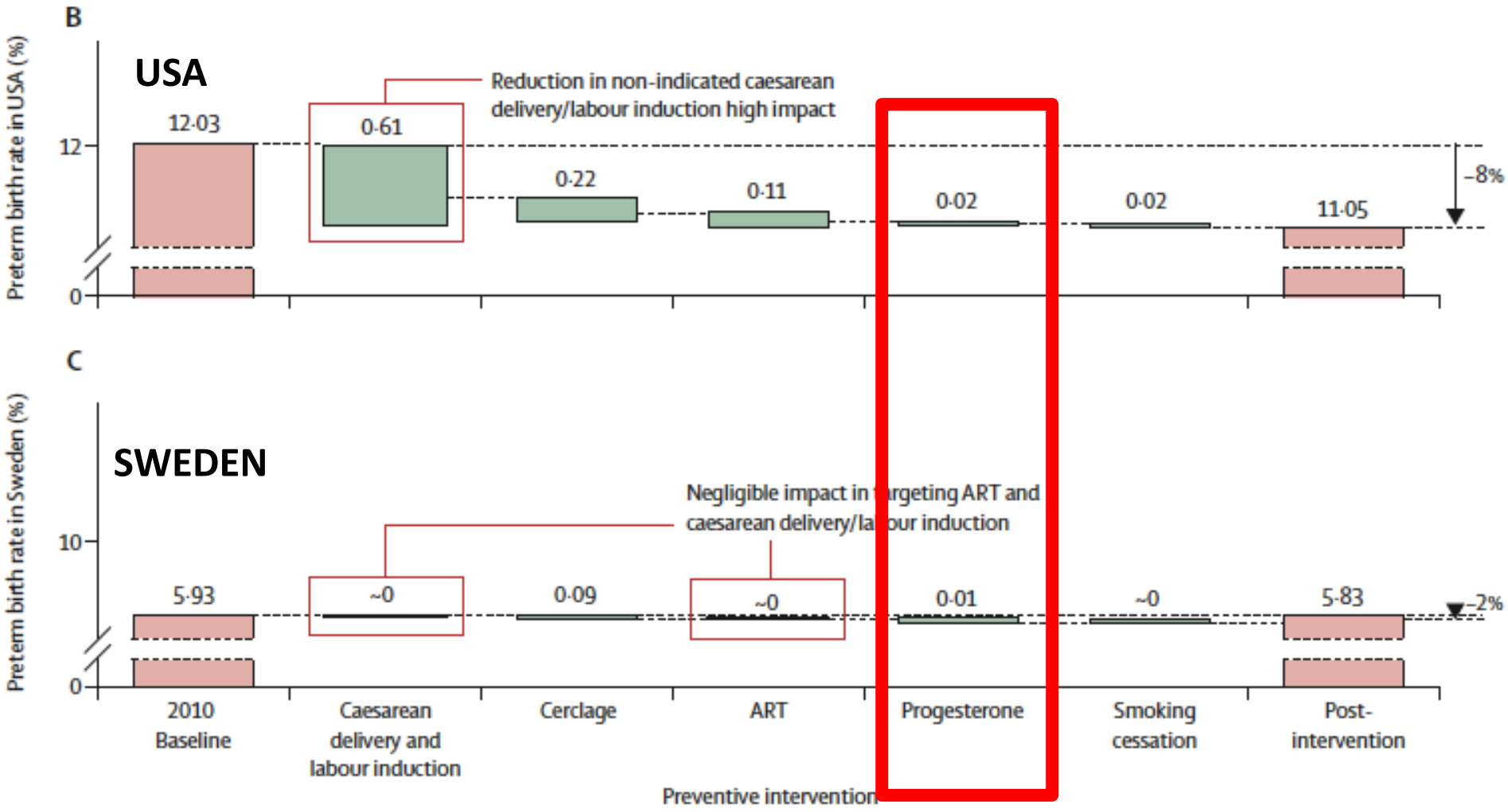

Figure 6: **Projected change from 2010 baseline preterm birth rate showing modelled contribution of the five selected interventions**

Cost-effectiveness of risk-based screening for cervical length to prevent preterm birth

Brett D. Einerson, MD, MPH; William A. Grobman, MD, MBA; Emily S. Miller, MD, MPH

American Journal of Obstetrics & Gynecology 2016;215:100.e1-7.

Prevalence of short cervix ≤20mm 0.85%
Relative risk reduction of delivery <35 weeks RR 0.6

2.2 million scans required
11 000 need treatment
About 900 PTD <35 weeks will be prevented

A reduction from 9.57% to 9.55% in PTD rates

HUGE EFFORTS
SMALL OVERALL EFFECT

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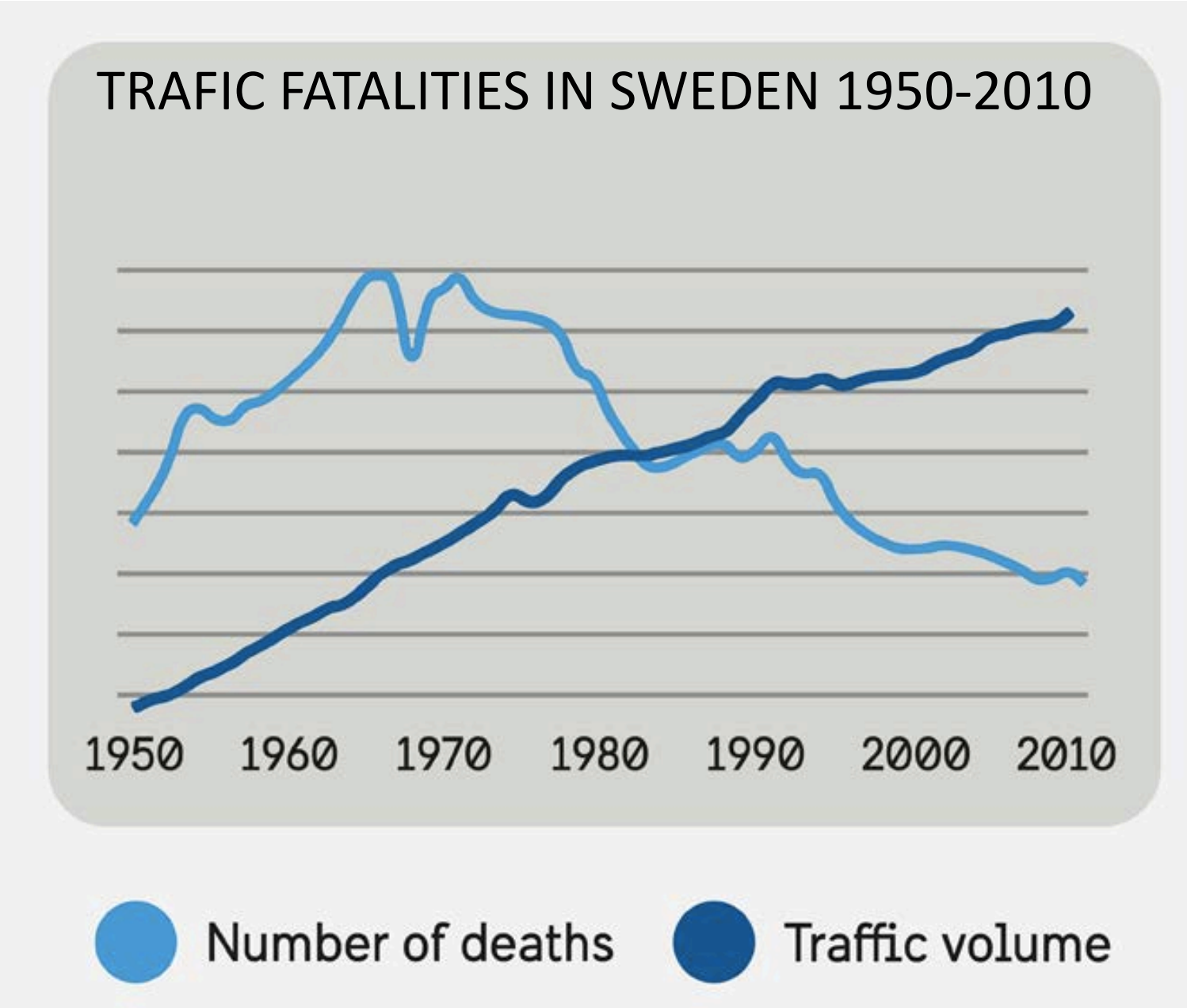
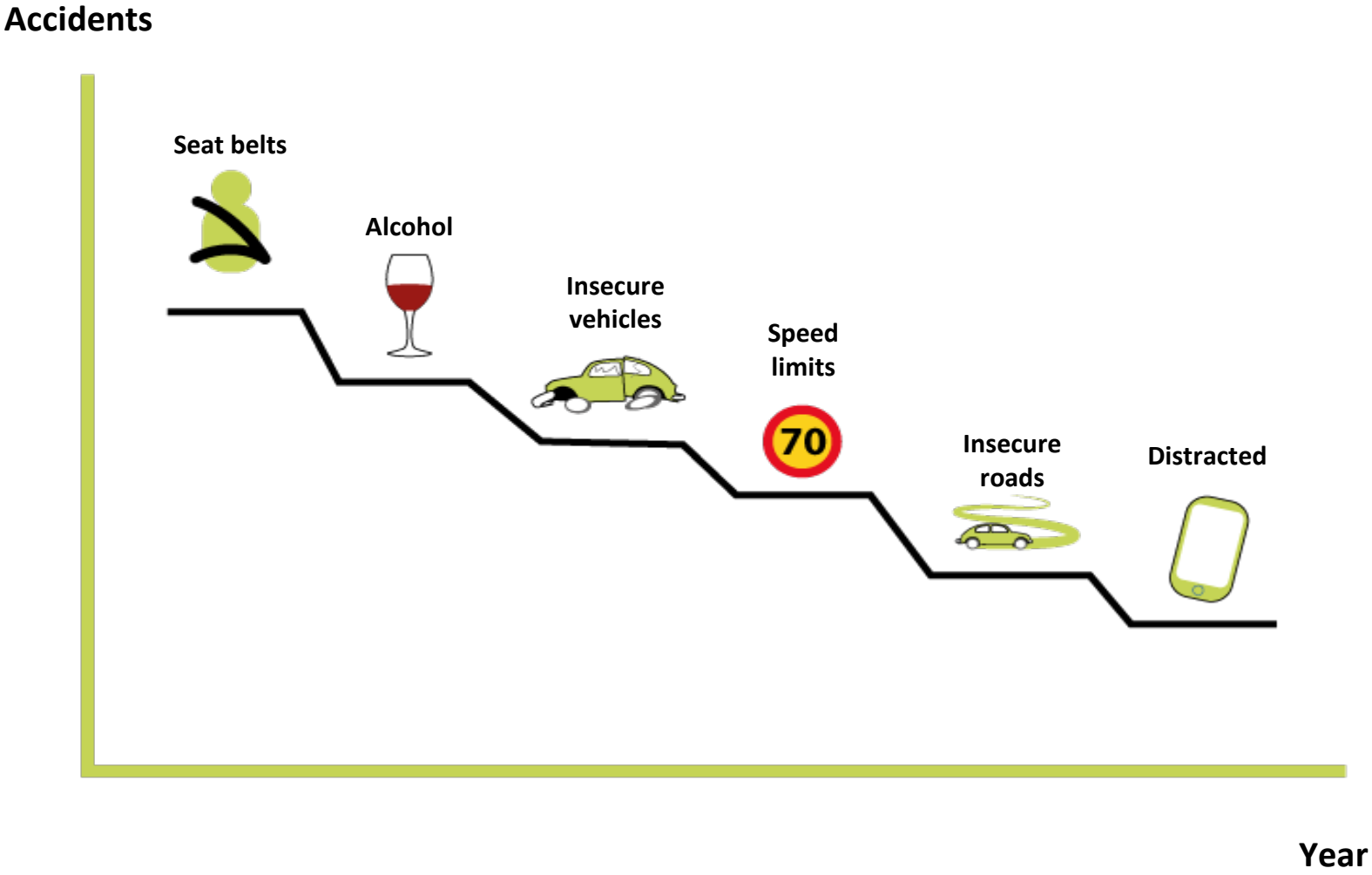
COMPLEX PHENOTYPE IS NOT A DEAD END

ANOTHER COMPLEX PHENOTYPE
IS TRAFIC FATALITIES
WITH A SUCCESSFUL REDUCTION



http://www.visionzeroinitiative.com/

TRAFIC FATALITIES REDUCTION STRATEGY



OVERVIEW OF THE TALK

5. RESEARCH IS NEEDED. WHICH RESEARCH TO PRIORITIZE?

6. QUALITATIVE CONTINOUS FOLLOW UP

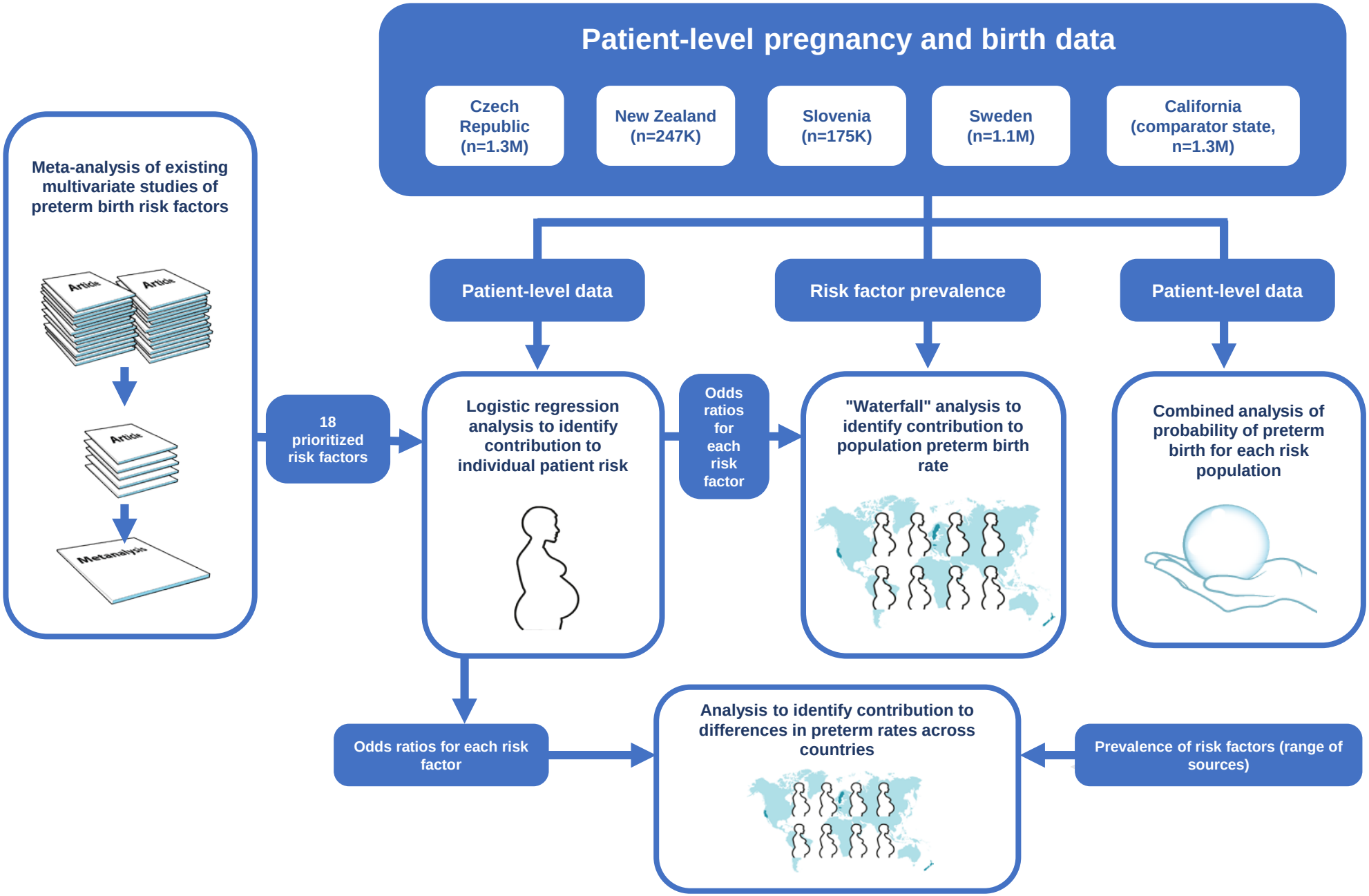
7. PROFESIONAL GUIDELINES AND GOVERNMENT ROLES

RESEARCH ARTICLE

Cross-Country Individual Participant Analysis of 4.1 Million Singleton Births in 5 Countries with Very High Human Development Index Confirms Known Associations but Provides No Biologic Explanation for 2/3 of All Preterm Births

David M. Ferrero[1], Jim Larson[1], Bo Jacobsson[4,13], Gian Carlo Di Renzo[3,10], Jane E. Norman[8], James N. Martin, Jr.[6], Mary D'Alton[7], Ernesto Castelazo[3], Chris P. Howson[2], Verena Sengpiel[4], Matteo Bottai[9], Jonathan A. Mayo[5], Gary M. Shaw[5], Ivan Verdenik[11], Nataša Tul[11], Petr Velebil[12], Sarah Cairns-Smith[1], Hamid Rushwan[3], Sabaratnam Arulkumaran[3], Jennifer L. Howse[2], Joe Leigh Simpson[2]*

PLOS ONE | DOI:10.1371/journal.pone.0162506 September 13, 2016



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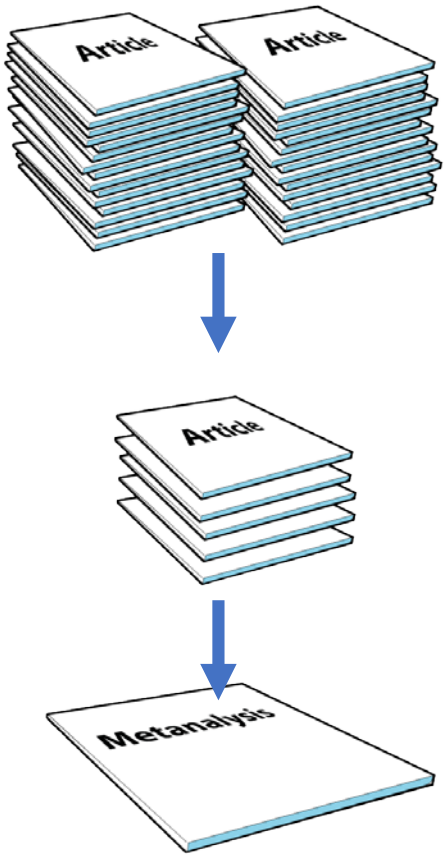
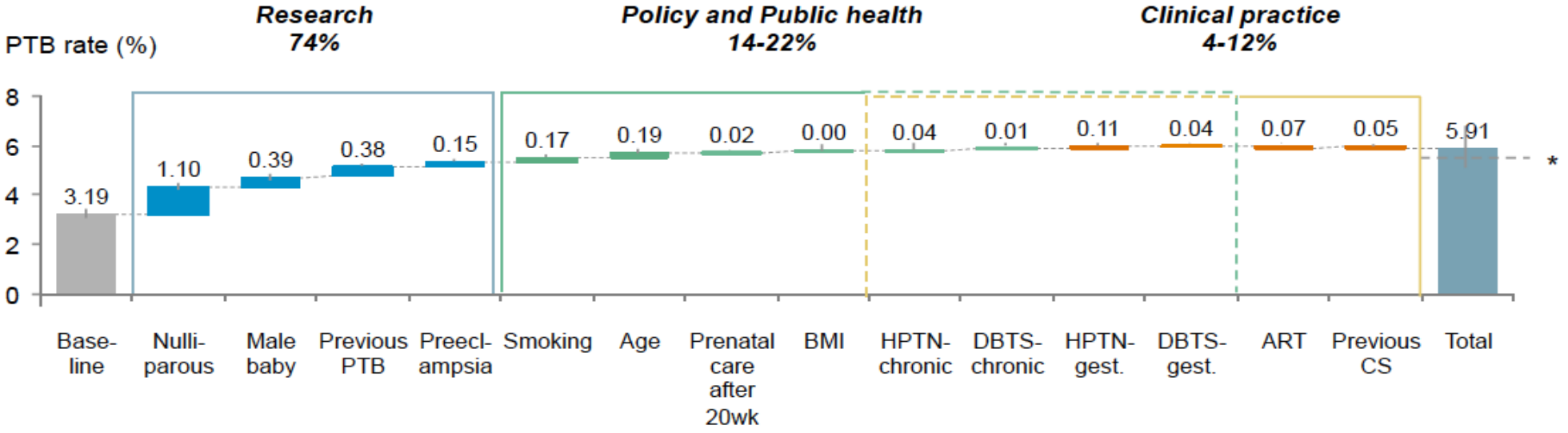
What is known?



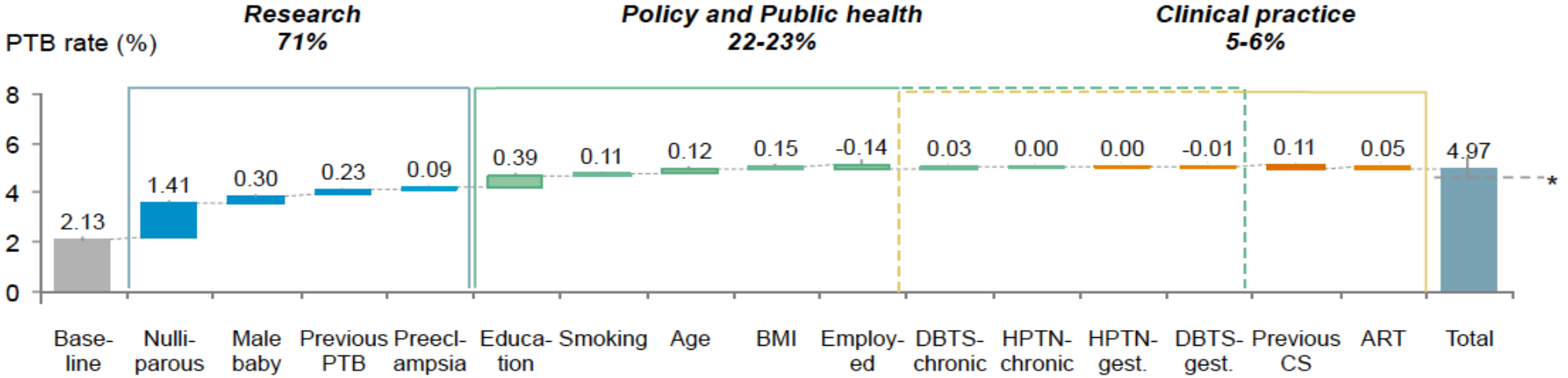
How much can these public health data explain differences in preterm birth rates in high income countries?

	Countries				Comparator US state
	Czech Rep.	New Zealand	Slovenia	Sweden	California
Previous PTB	5.2**	5.7**	4.6**	6.0**	5.0**
Preeclampsia	4.8**	3.4**	2.8**	5.7**	4.2**
Diabetes (chronic)	3.4**		1.9**	3.6**	
Hypertension (chronic)			2.1**	1.7**	3.0**
Maternal Age					
Age > 40	1.8**	1.3**	1.6**	1.4**	1.5**
Age 35-40	1.4**	1.2**	1.4**	1.2**	1.3**
Age < 20	1.1**	1.1	1.1	0.9*	1.0
Nulliparous	1.5**	1.4**	1.6**	2.1**	1.2**
ART			1.7**	1.3**	1.7**
Drug use (illicit)	1.7**				
Ethnicity					
Ethnicity (other)					1.7**
Ethnicity (Non-Hispanic Black)					1.6**
Ethnicity (Asian)		1.0			1.3**
Ethnicity (Hispanic)					1.2**
Ethnicity (Pacific P)		0.9**			
Ethnicity (MELAA)		1.1			
Ethnicity (Maori)		1.0			
Smoking	1.3**	1.6**	1.3**	1.3**	1.4**
Diabetes (gestational)	1.3**	1.9**	1.3*	0.9*	1.3**
Hypertension (gestational)	1.3**		1.6**	0.6**	
BMI					
BMI (underweight)			1.4**	1.3**	1.3**
BMI (overweight)			0.9	1.0**	1.0
BMI (obese – class I)			0.9	1.1**	1.0**
BMI (obese – class II & III)			0.8	1.3**	1.1**

Slovenia



Sweden



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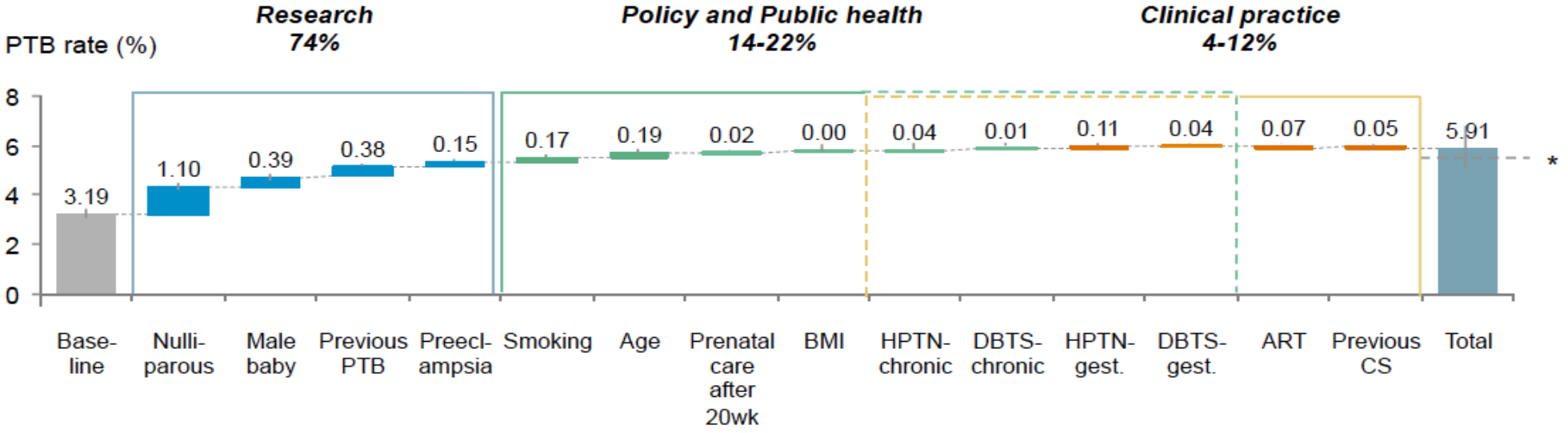
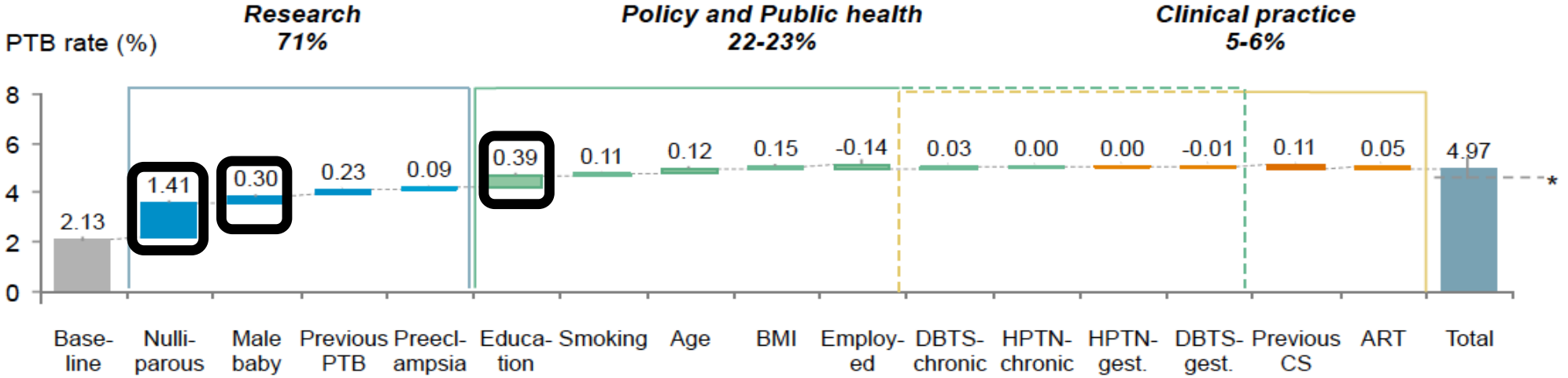
Slovenia



Sweden



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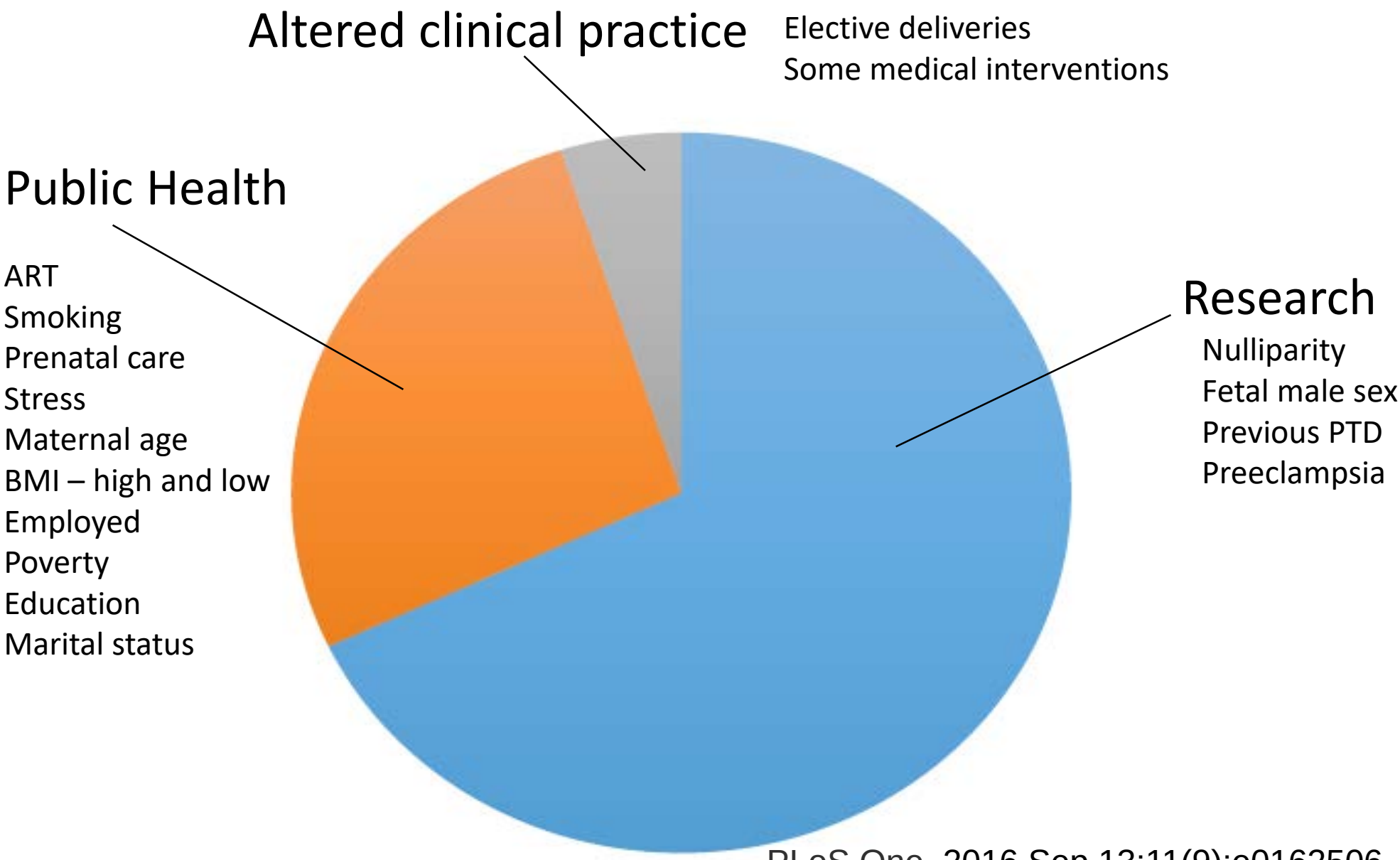
AREAS OF INTERVENTION



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OVERVIEW OF THE TALK

5. RESEARCH IS NEEDED. WHICH RESEARCH TO PRIORITIZE?

6. CONTINOUS QUALITATIVE FOLLOW UP

7. PROFESIONAL GUIDELINES AND GOVERNMENT ROLES

Mandatory registers – continuous validation of data and interventions

OVERVIEW OF THE TALK

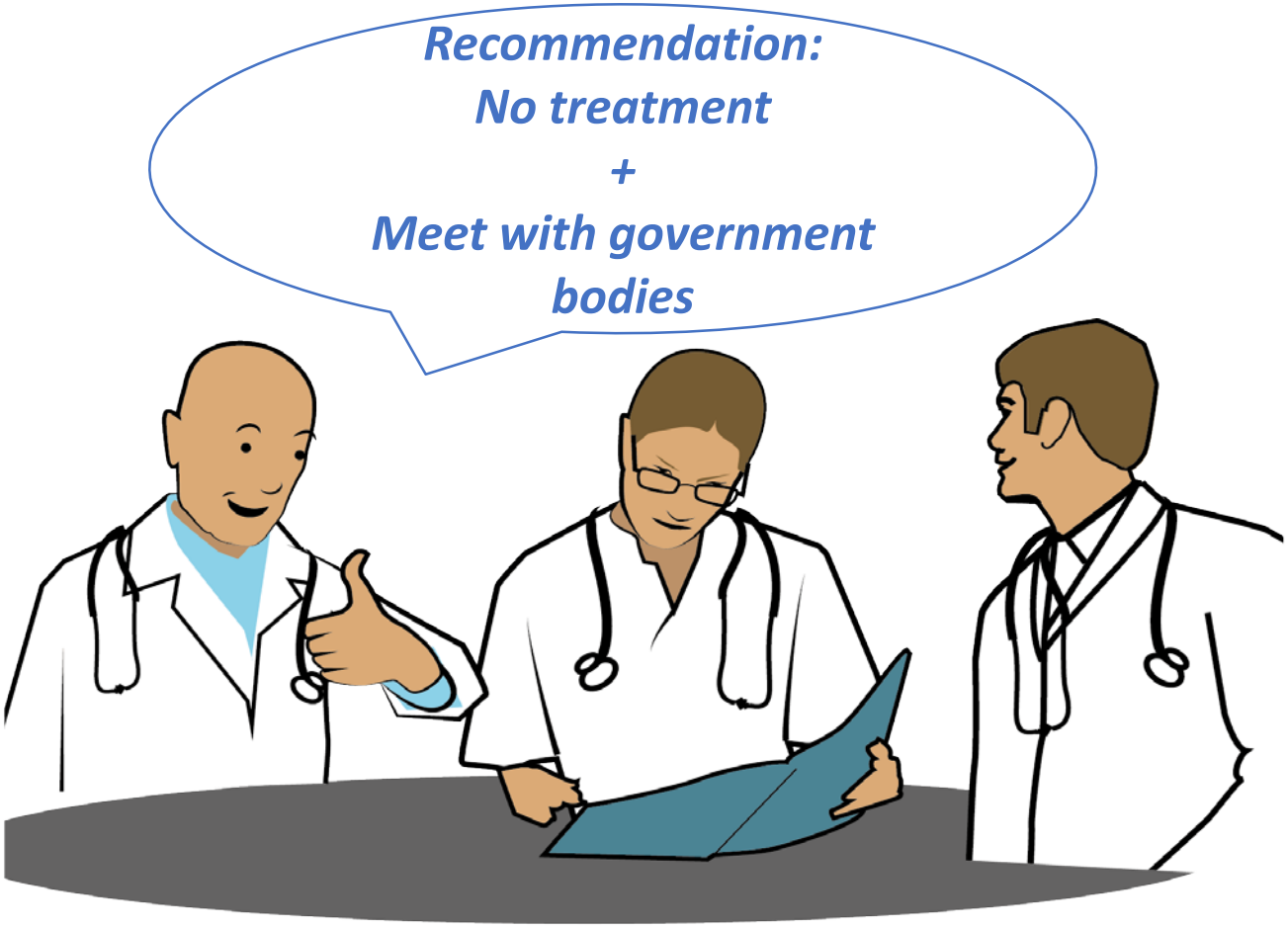
5. WHAT TO DONE WITH CURRENT KNOWLEDGE? LOW HANGING FRUITS.

6. RESEARCH IS NEEDED. WHICH RESEARCH TO PRIORITIZE?

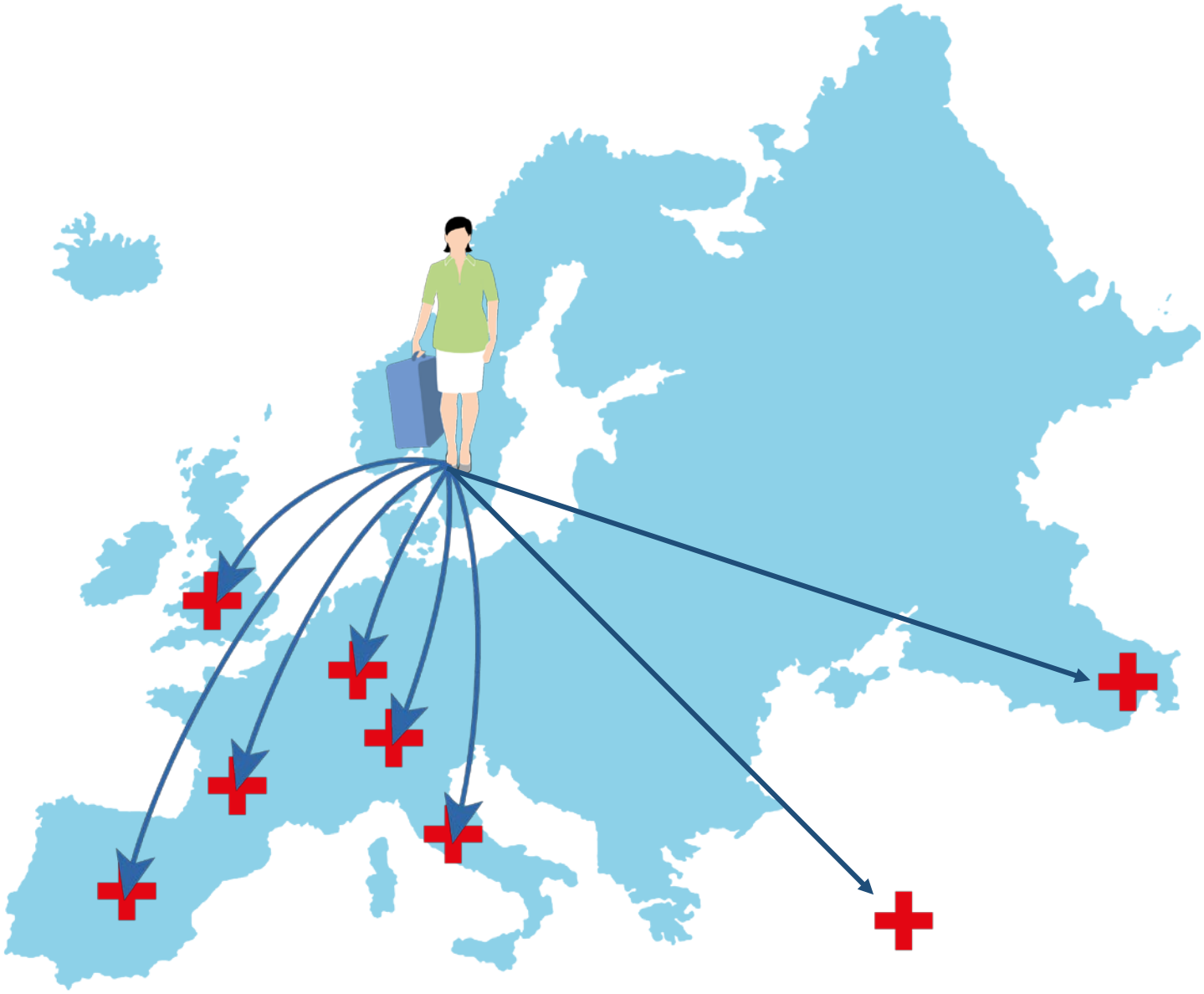
7. QUALITATIVE CONTINOUS FOLLOW UP

8. PROFESIONAL GUIDELINES AND GOVERMENTAL ROLES

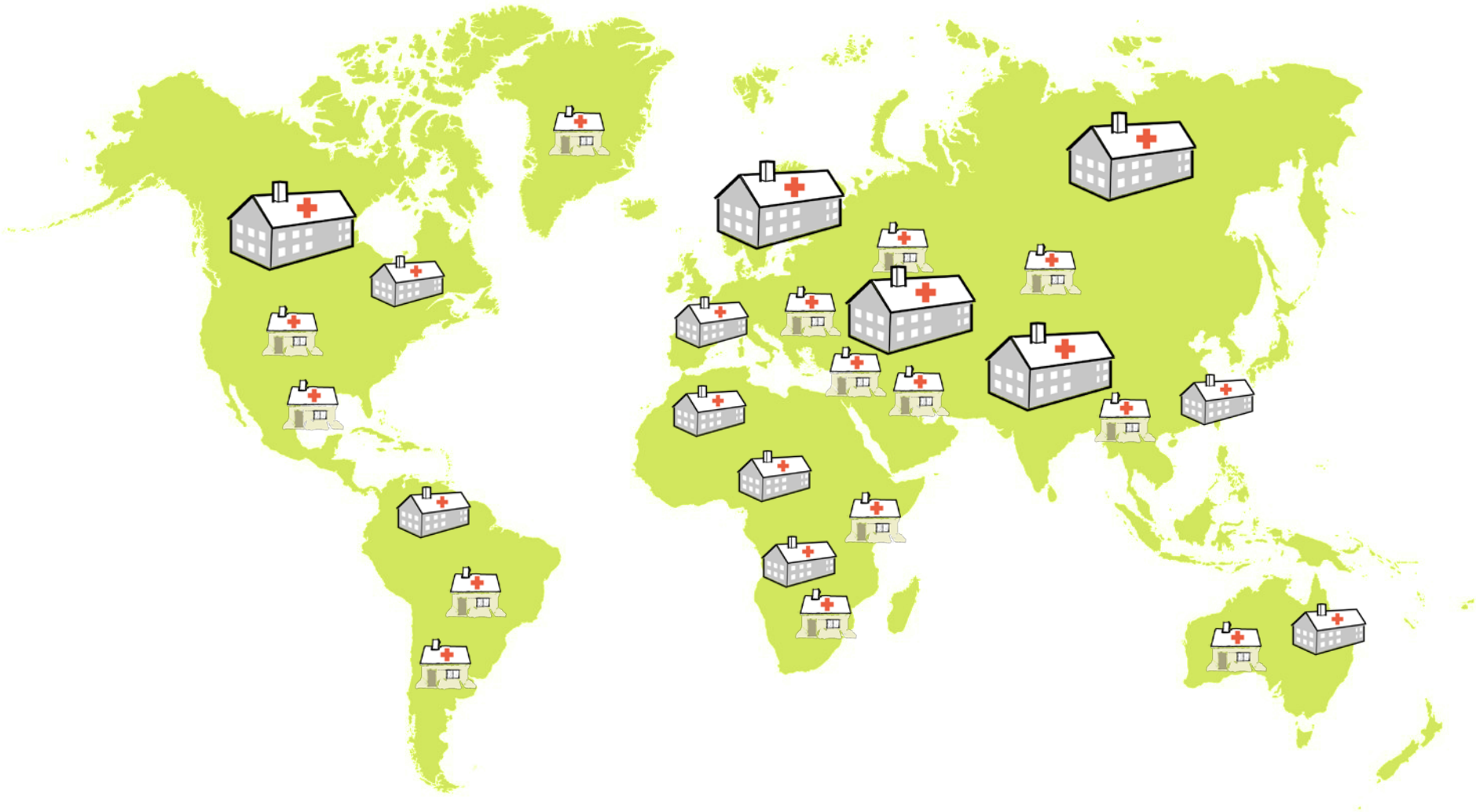
Professional organizations issues guidelines + engage in society building



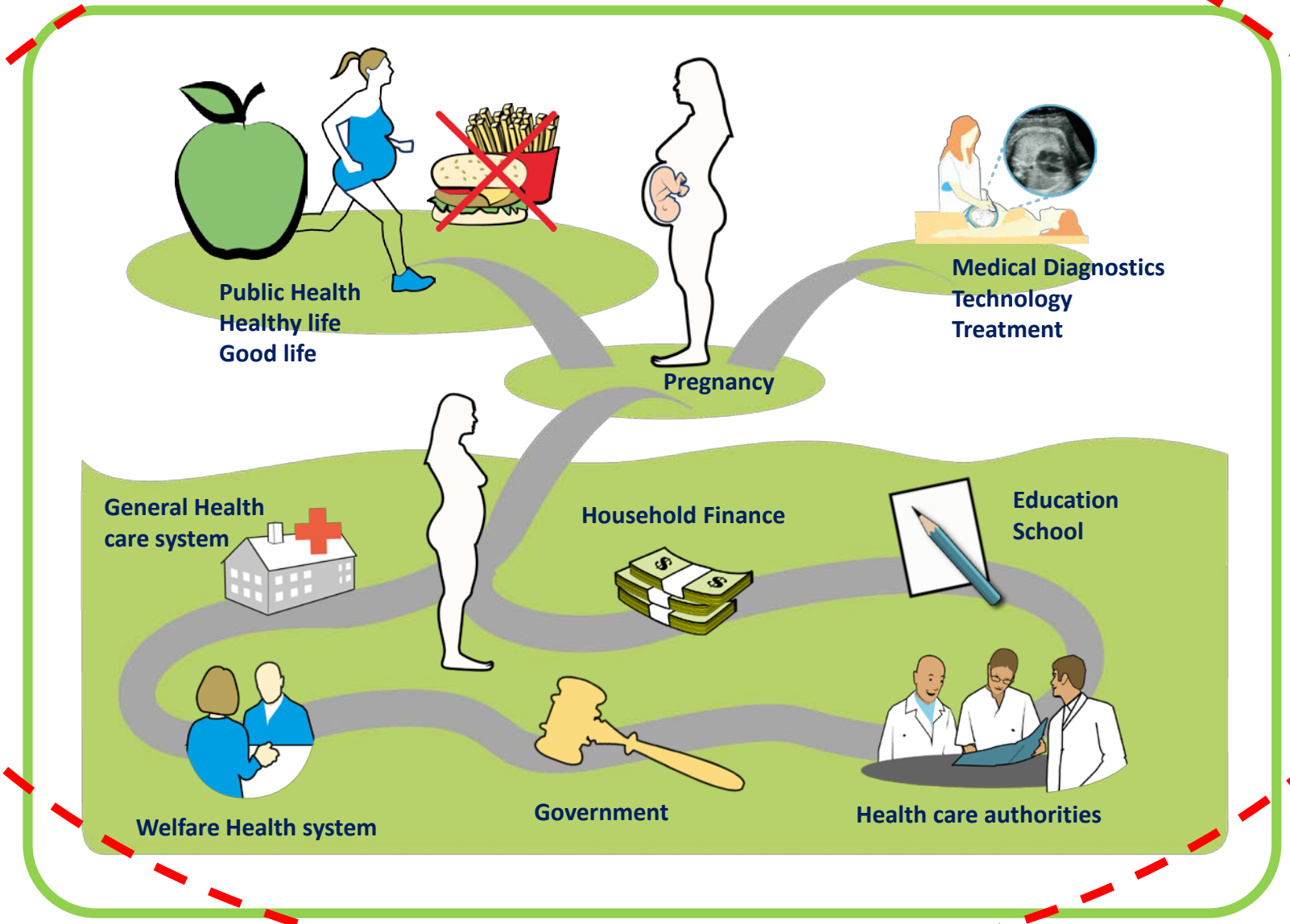
Medical tourism



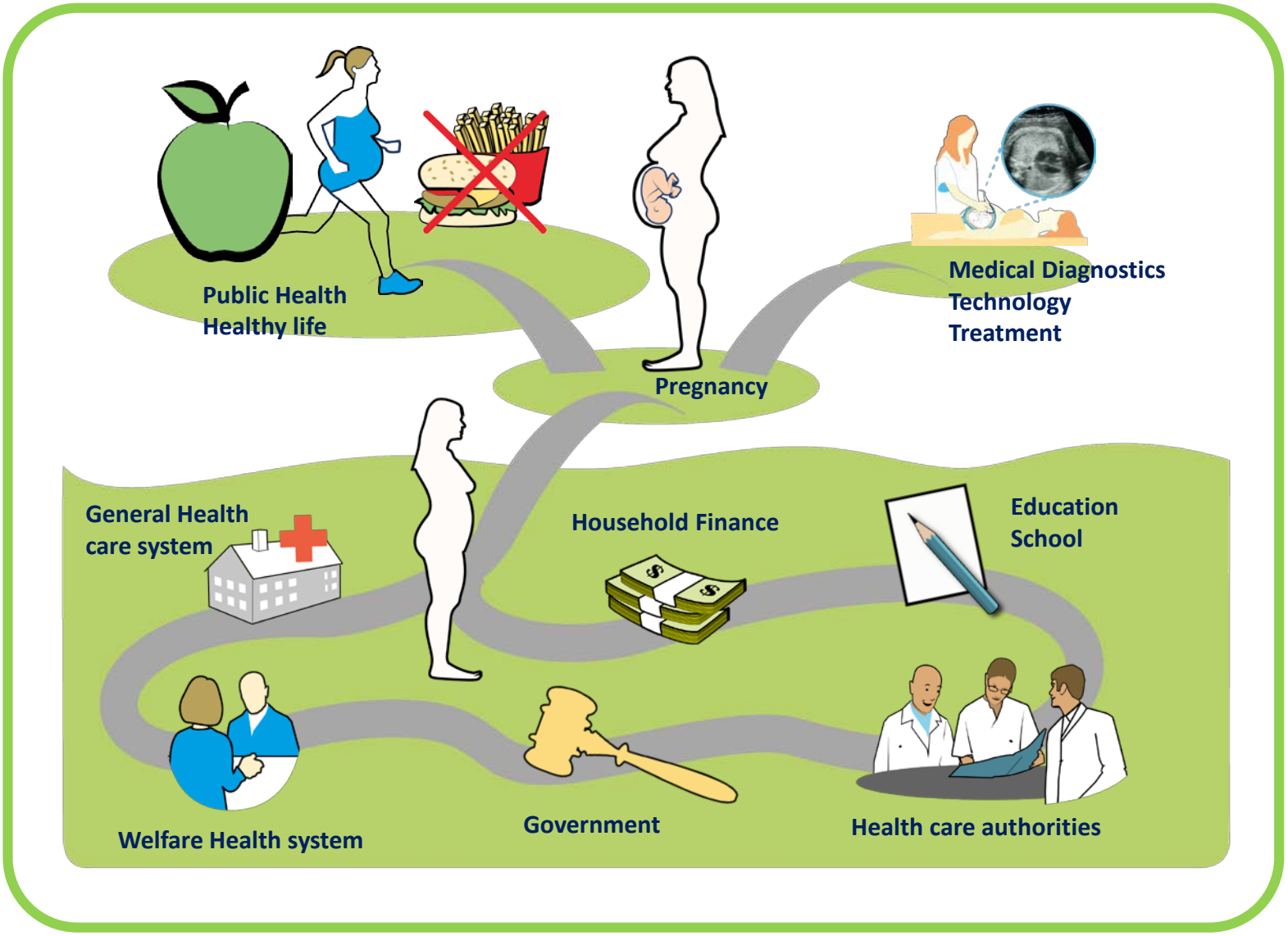
We also need to look at health care organization/government issues



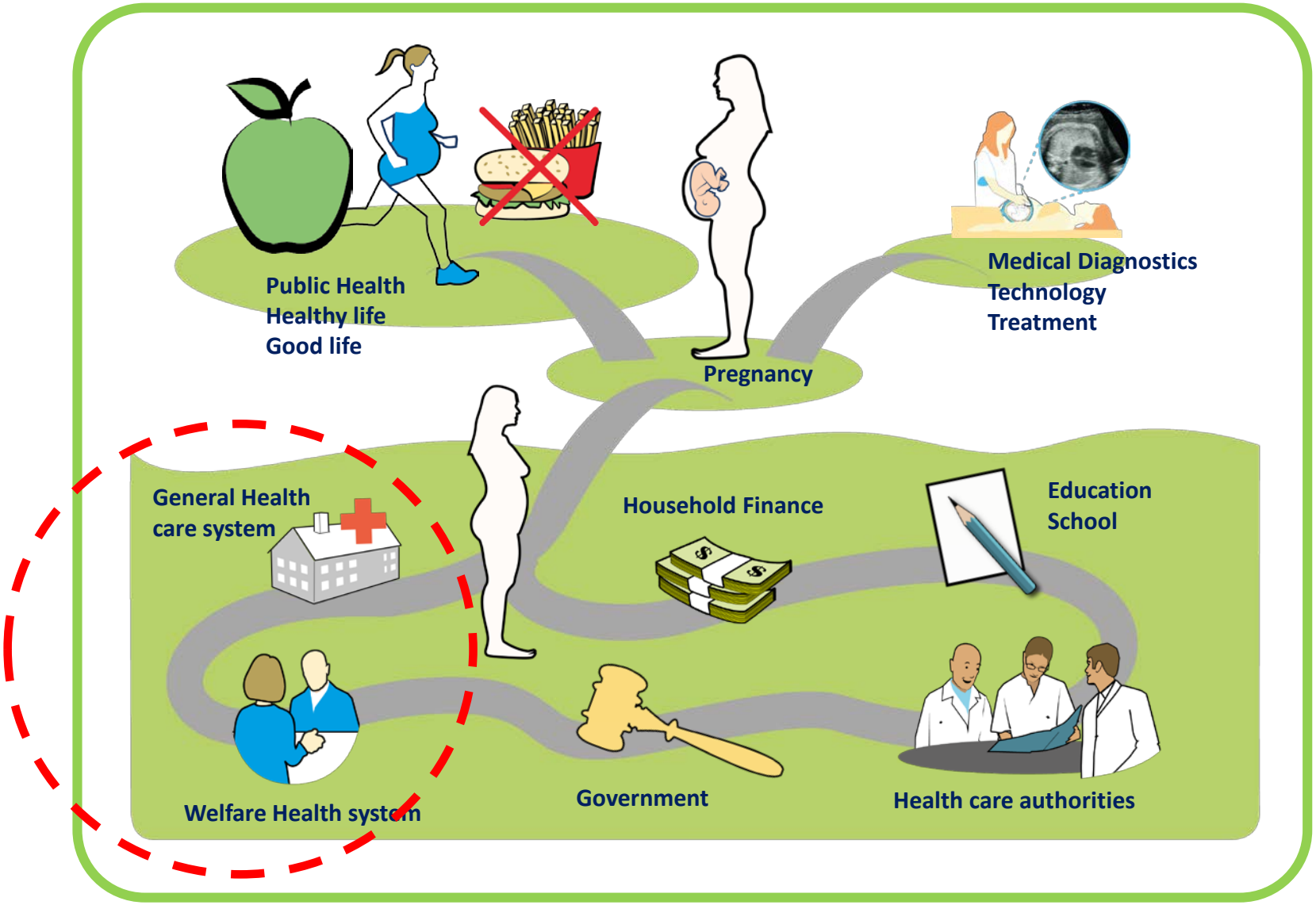
Research and constant simultaneous validation



Research and constant simultaneous registration and validation



Research and constant simultaneous registration and validation



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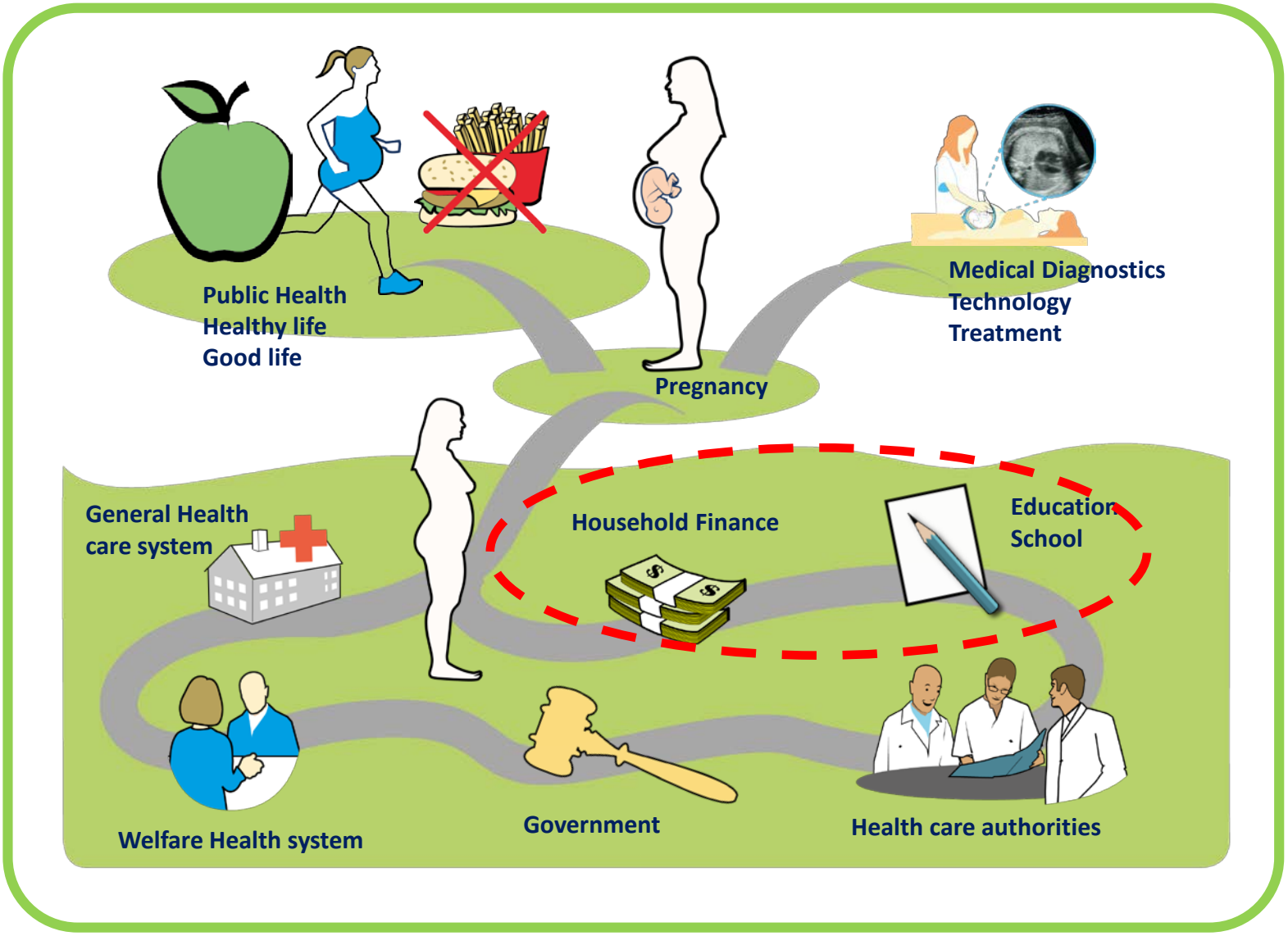

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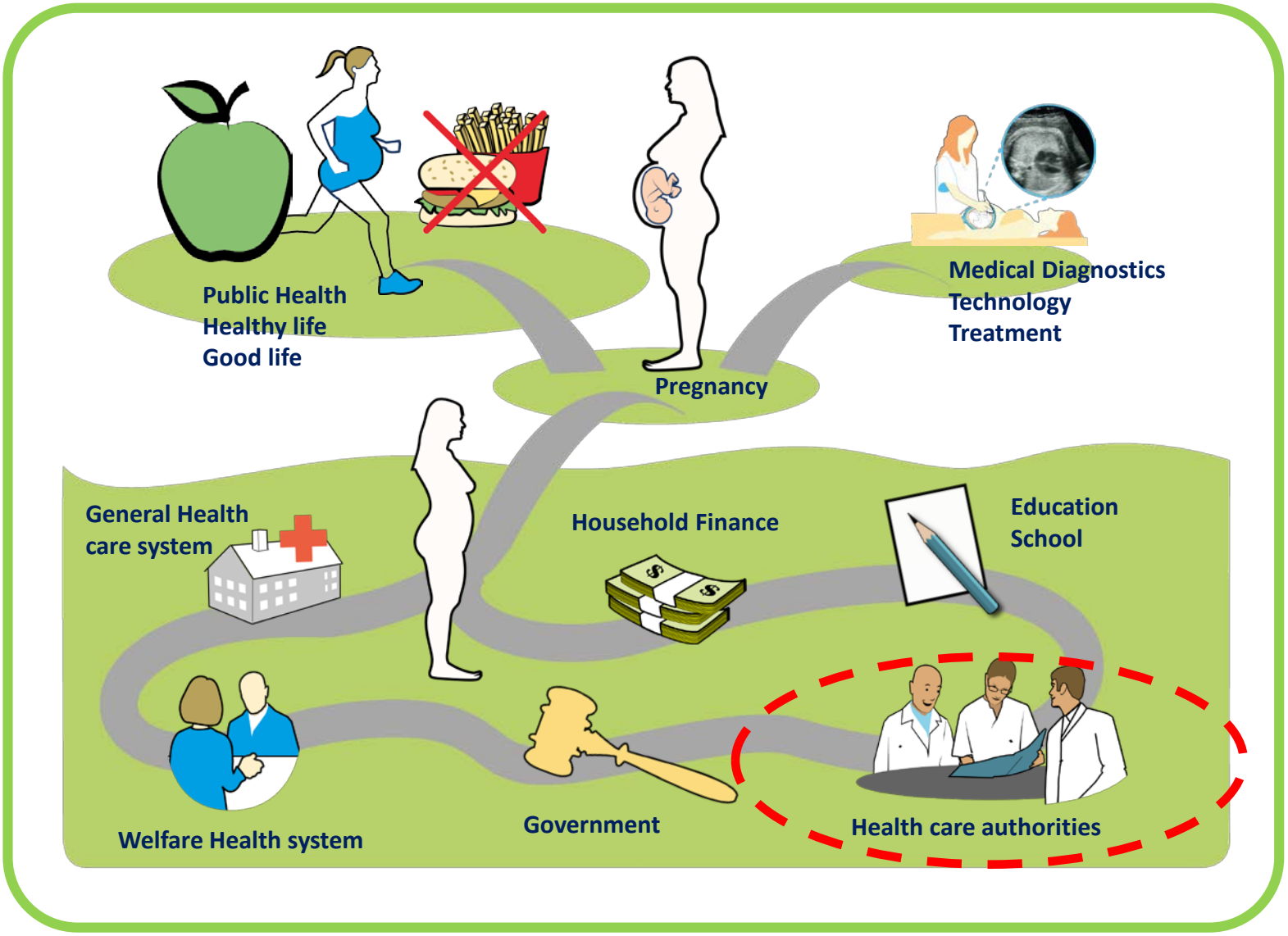
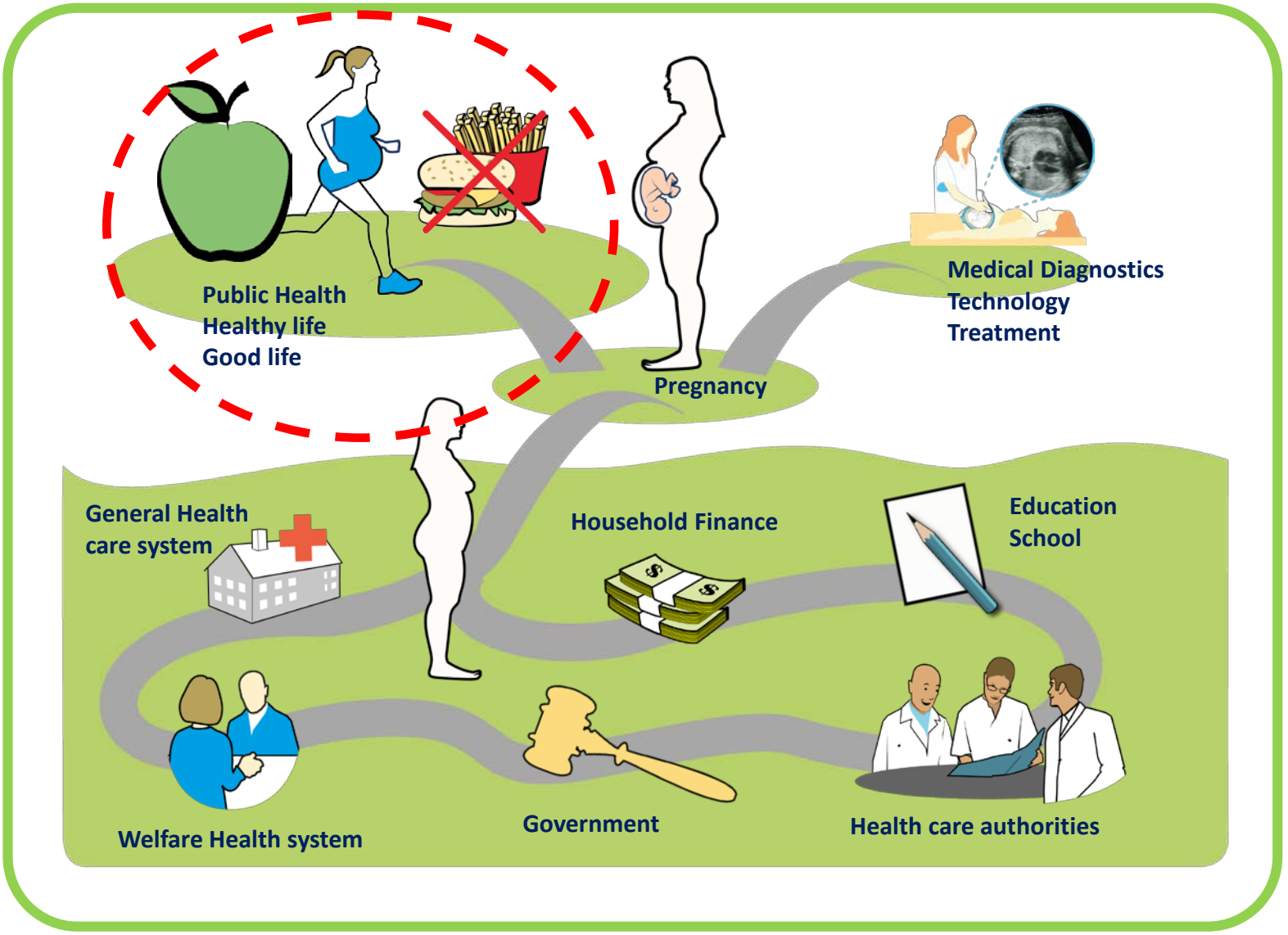
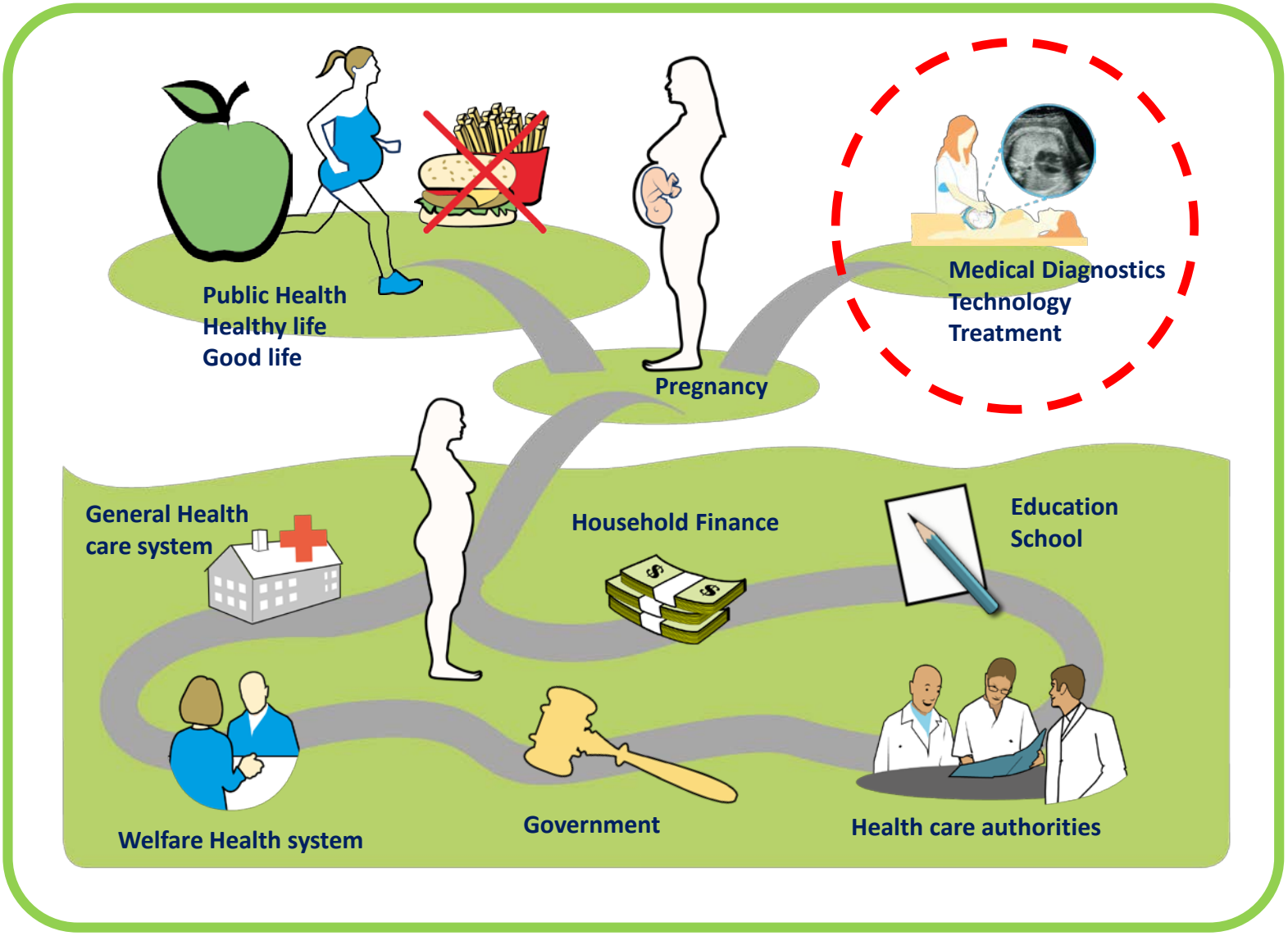


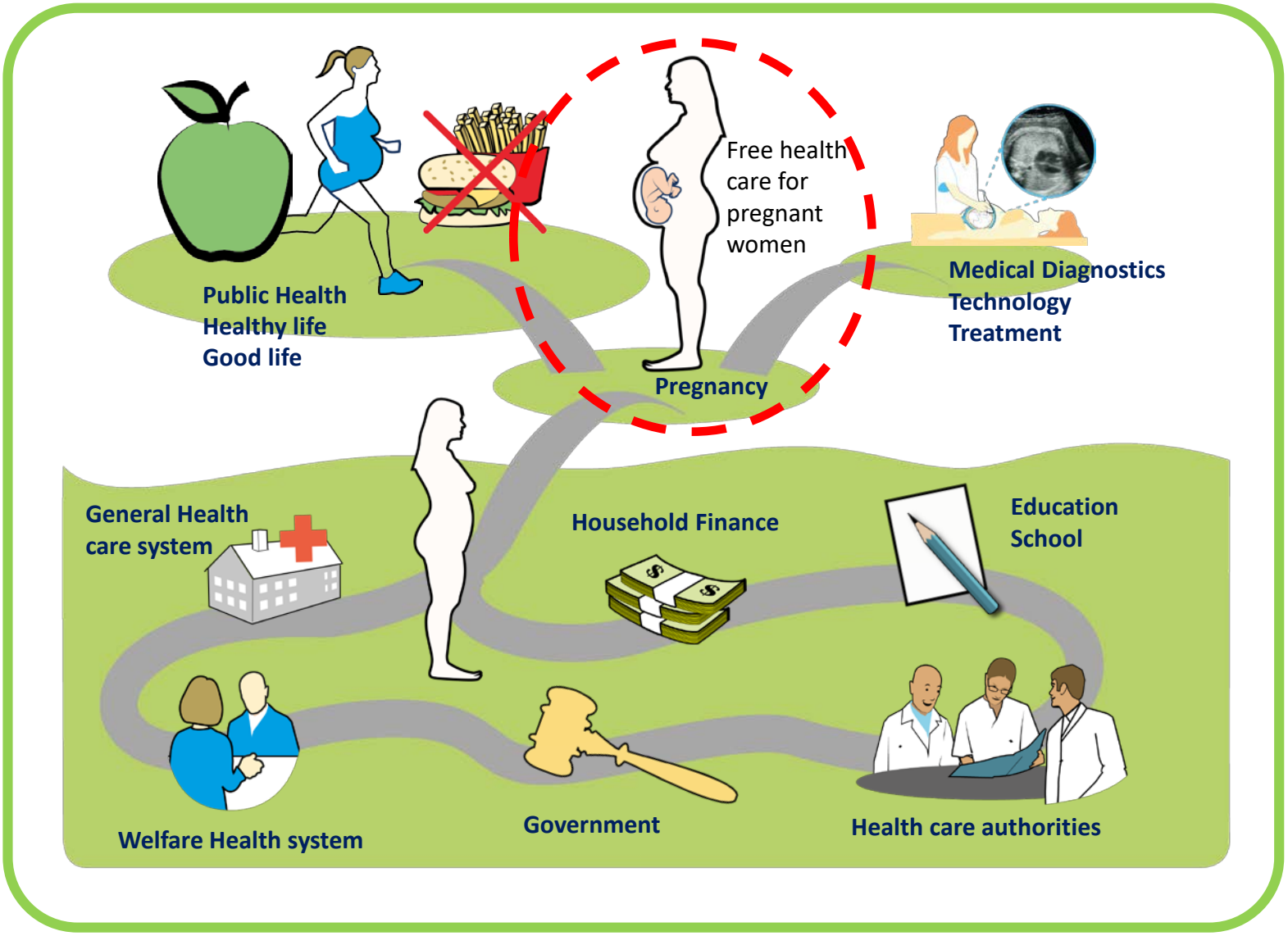
Research and constant simultaneous registration and validation



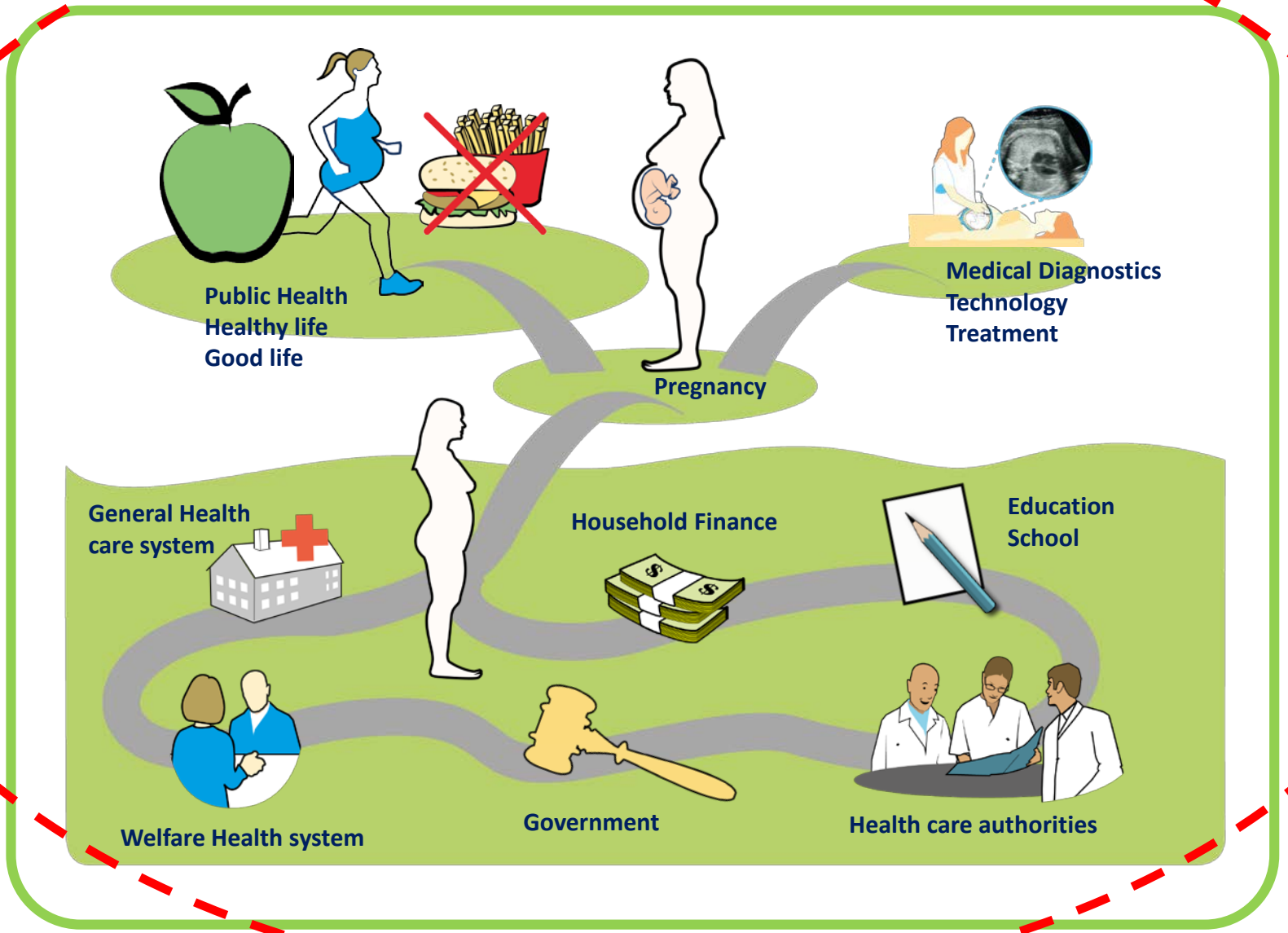
Research and constant simultaneous registration and validation



Research and constant simultaneous registration and validation



Research and constant simultaneous registration and validation



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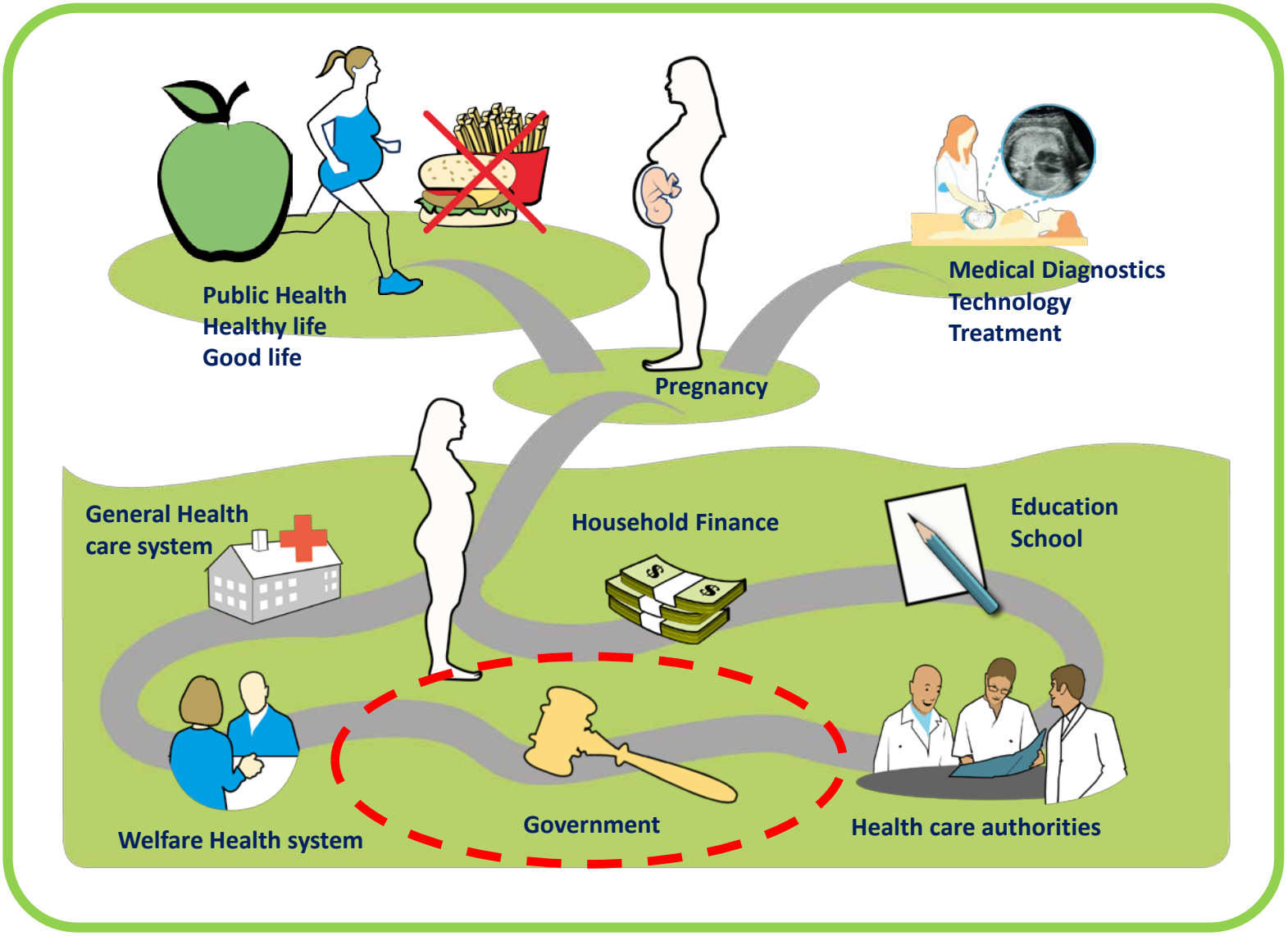
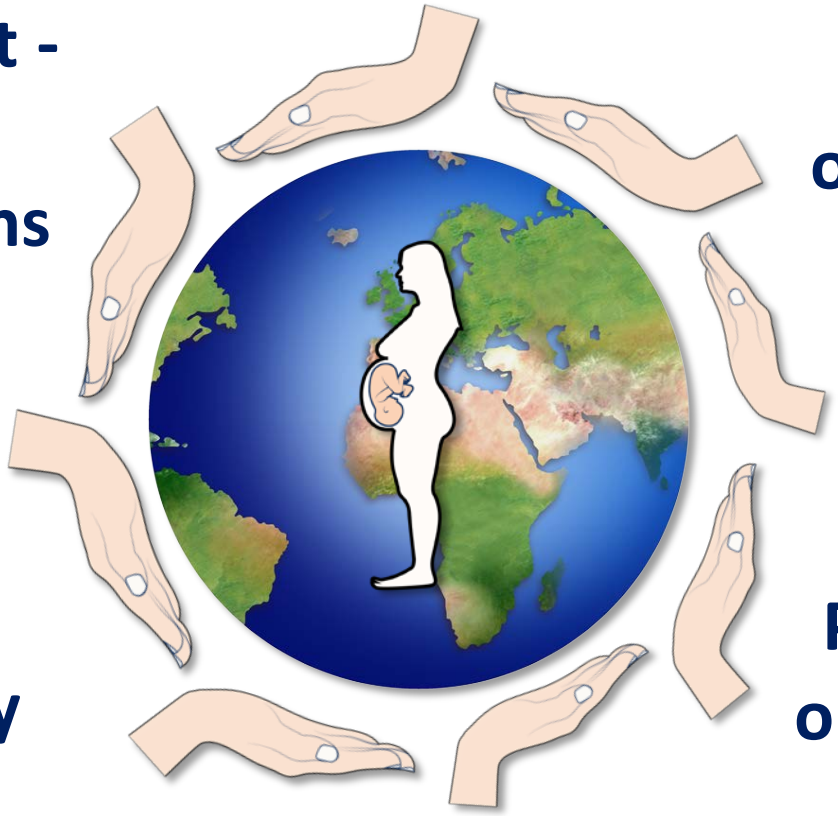


A joint huge effort on women´s health

Government - Funding organizations



Parents organizations: EFCINI

Industry

Professional organizations: FIGO et al

Thanks

Thanks

Especially to Dr Teresa Cobo