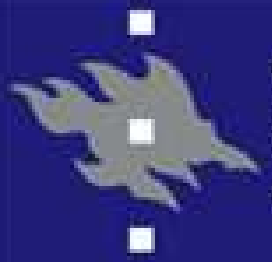


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HELSINGIN YLIOPISTO
HELSINGFORS UNIVERSITET
UNIVERSITY OF HELSINKI

Early Nutrition and Risk of Type 1 Diabetes – Experiences from the TRIGR Study

Mikael Knip, M.D., Ph.D.

Hospital for Children and Adolescents

EARLY FEEDING MODEL



Breasts for the men



TRIGR

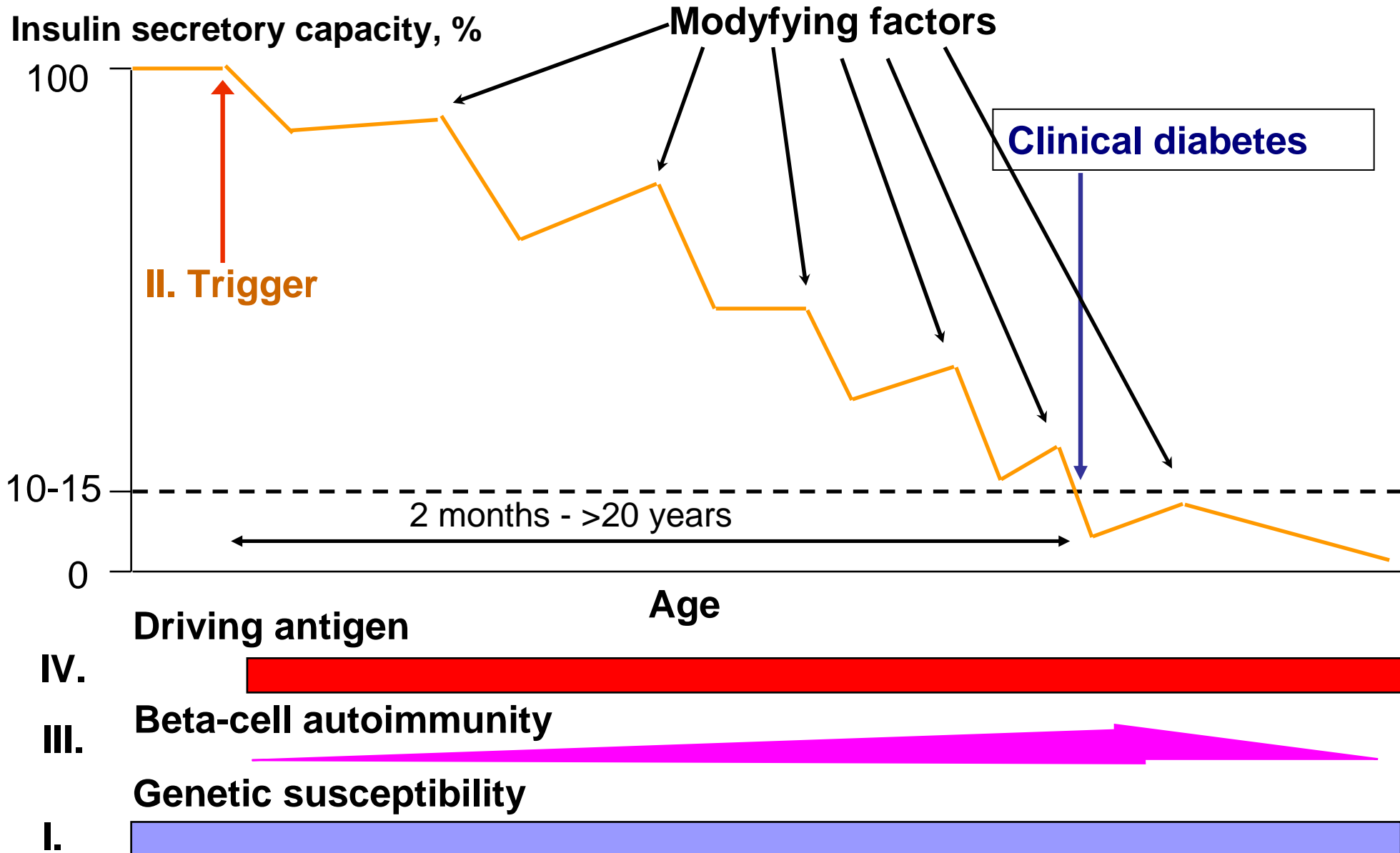
stands for

Trial to Reduce IDDM in the

Genetically at Risk



PATHOGENESIS OF TYPE 1 DIABETES





EARLY FEEDING AND TYPE 1 DIABETES

RISK FACTORS

- Short breastfeeding
- Early exposure to cow's milk proteins
- Early exposure to cereals
- Early exposure to fruits and berries
- Early exposure to root vegetables
- Lack of supplementation with vitamin D in infancy
- Heavy weight and rapid weight gain in infancy

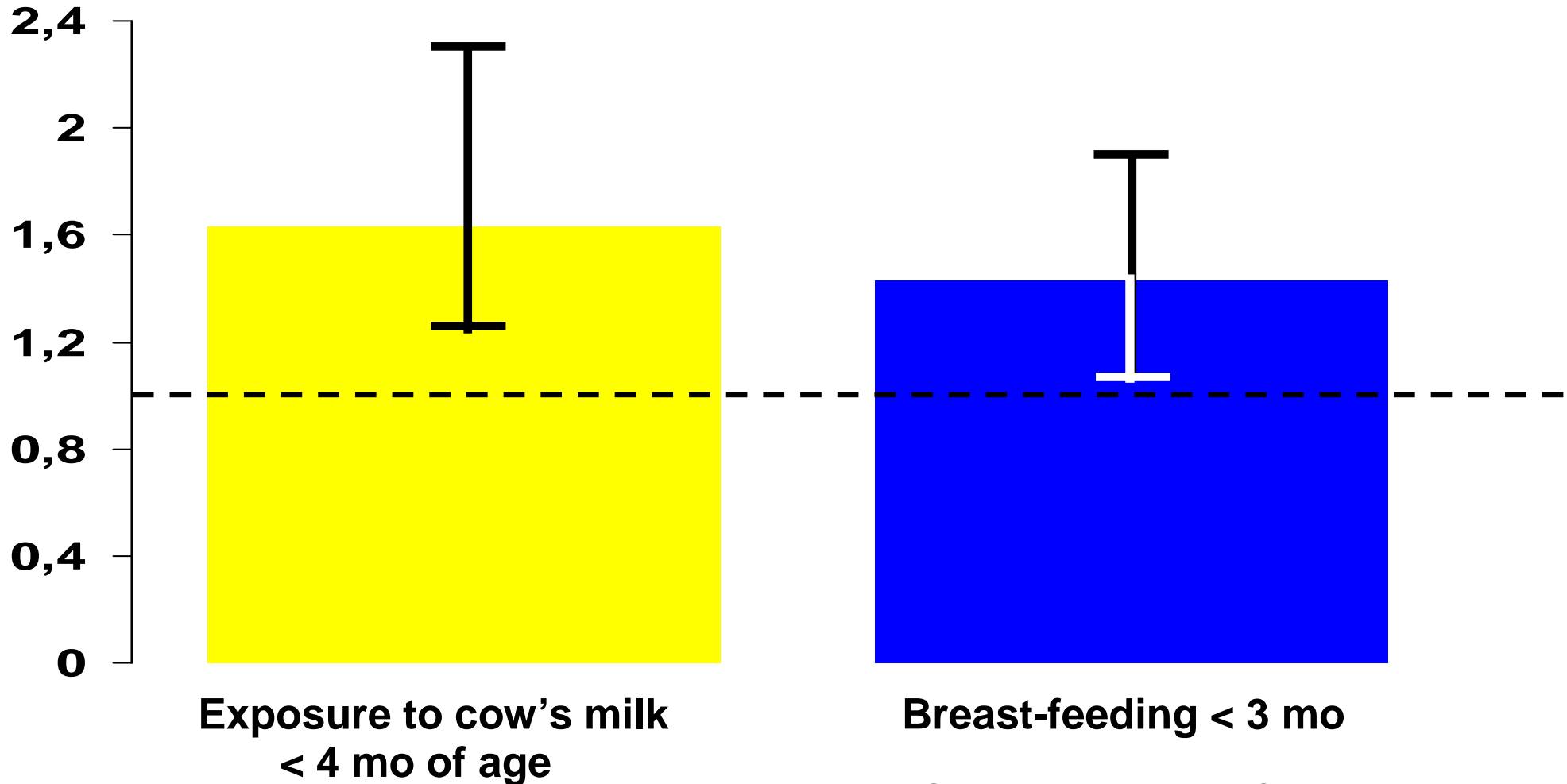


COW'S MILK PROTEINS AS AN ETIOLOGIC AGENT IN T1D

- **Animal feeding studies**
- **Immunological studies in animal models**
- **Human epidemiologic and clinical studies**
- **Human immunological studies**

RELATIVE RISK OF TYPE 1 DIABETES IN RELATION TO EARLY EXPOSURE TO COW'S MILK AND SHORT DURATION OF BREAST-FEEDING

Odds ratio



Gerstein, *Diabetes Care* 1994;17:13-19



TYPE OF STUDIES USED TO DEFINE THE RELATION BETWEEN BREASTFEEDING/EXPOSURE TO COW'S MILK AND T1D

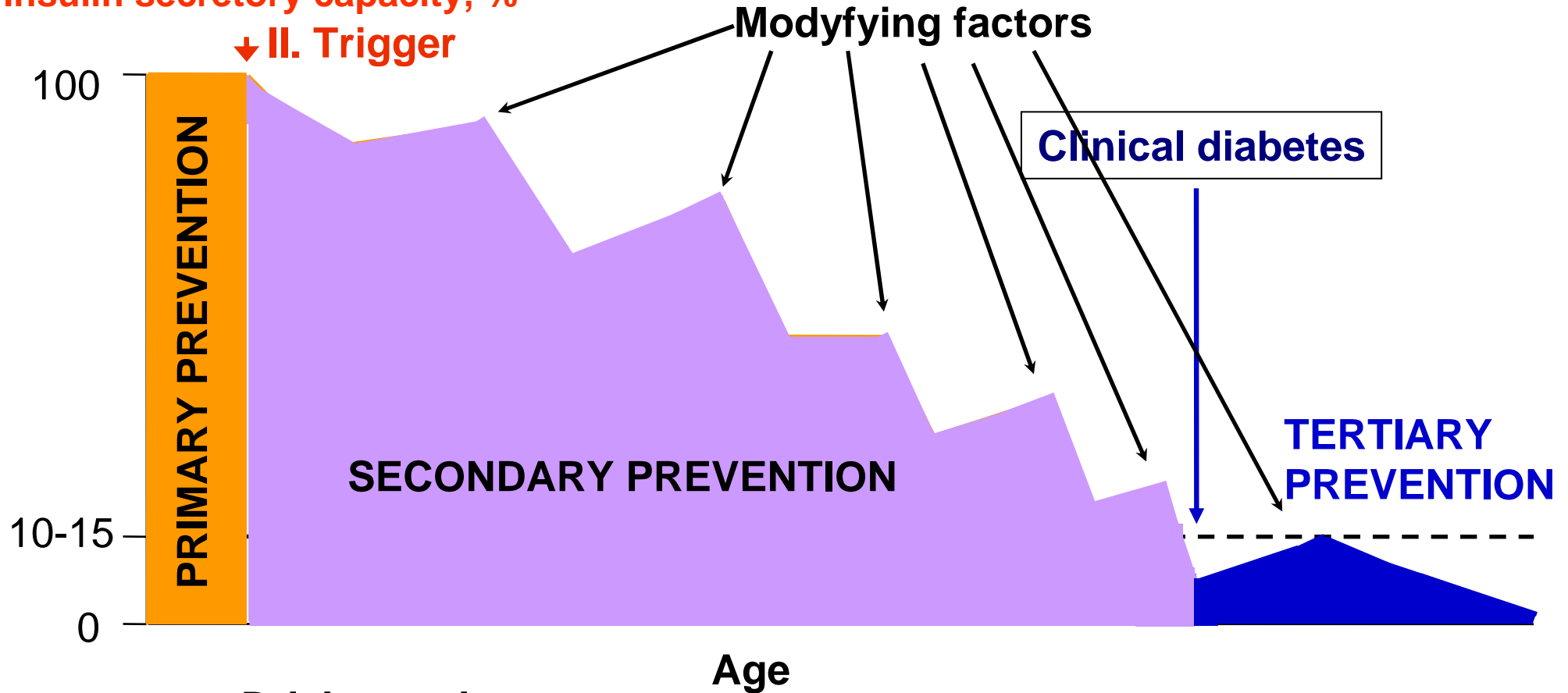
TYPE OF STUDY	BREASTFEEDING	EARLY EXPOSURE TO COW'S MILK
Ecological studies	-, 0	+
Retrospective case-control studies	-, 0, +	0, +
Prospective case-control studies	-, 0, +	0, +
Intervention study		+

- = protective effect; 0 = no effect; + = predisposing effect

PREVENTION OF T1D

Insulin secretory capacity, %

↓ II. Trigger



Driving antigen

IV.

Beta-cell autoimmunity

III.

Genetic susceptibility

I.





BACKGROUND OF TRIGR PILOT AND FULL-SCALE TRIGR

- **EARLY EXPOSURE TO COMPLEX DIETARY
PROTEINS MAY INCREASE THE RISK OF BETA-
CELL AUTOIMMUNITY AND TYPE 1 DIABETES IN
CHILDREN WITH INCREASED GENETIC DISEASE
SUSCEPTIBILITY**





PILOT RESEARCH QUESTION

- IS IT POSSIBLE TO REDUCE THE FREQUENCY OF DIABETES-ASSOCIATED AUTOANTIBODIES BY EXCLUDING DIETARY COW'S MILK PROTEINS OVER THE FIRST 6-8 MONTHS OF LIFE IN SUBJECTS AT INCREASED RISK OF TYPE 1 DIABETES?**

STUDY POPULATION

- **TWO HUNDRED THIRTY (230) INFANTS FROM DIABETIC FAMILIES:**
 - 85 mothers with diabetes (37%)
 - 100 fathers with diabetes (43%)
 - 35 siblings with diabetes (15%)
 - 10 families with more than one affected family member (4%)

- **HLA GENOTYPES:**

- DQB1*02/0302	51 (22%)
- DQB1*0302/x	92 (40%)
- DQB1*02/y	87 (38%)

- **FOLLOW-UP TIME: mean 7.5 years (range 3 months – 10 years)
median 10 years**



QUESTION IN TRIGR PROPER

- IS IT POSSIBLE TO REDUCE**
 - (i) THE FREQUENCY OF DISEASE-ASSOCIATED AUTO-ANTIBODIES AND/OR CLINICAL DIABETES BY THE AGE OF 6 YEARS AND**
 - (ii) THE CUMULATIVE INCIDENCE OF DIABETES BY THE AGE OF 10 YEARS**
- BY WEANING TO A HIGHLY HYDROLYZED FORMULA OVER THE FIRST 6-8 MONTHS OF LIFE?**



TRIGR: GENERAL DESIGN

- **International, double-blinded, prospective, placebo-controlled intervention trial**
- **Targets children who have a first-degree relative with type 1 diabetes and who carry HLA genotypes conferring increased disease risk**
- **Compares casein hydrolysate formula to conventional cow's milk based infant formula**



Nutramigen

(Mead Johnson Nutritionals)

Casein hydrolysate

Molecular weight	%
> 1,000 daltons	5.4
> 2,000 daltons	0.3



INCREASED GENETIC RISK

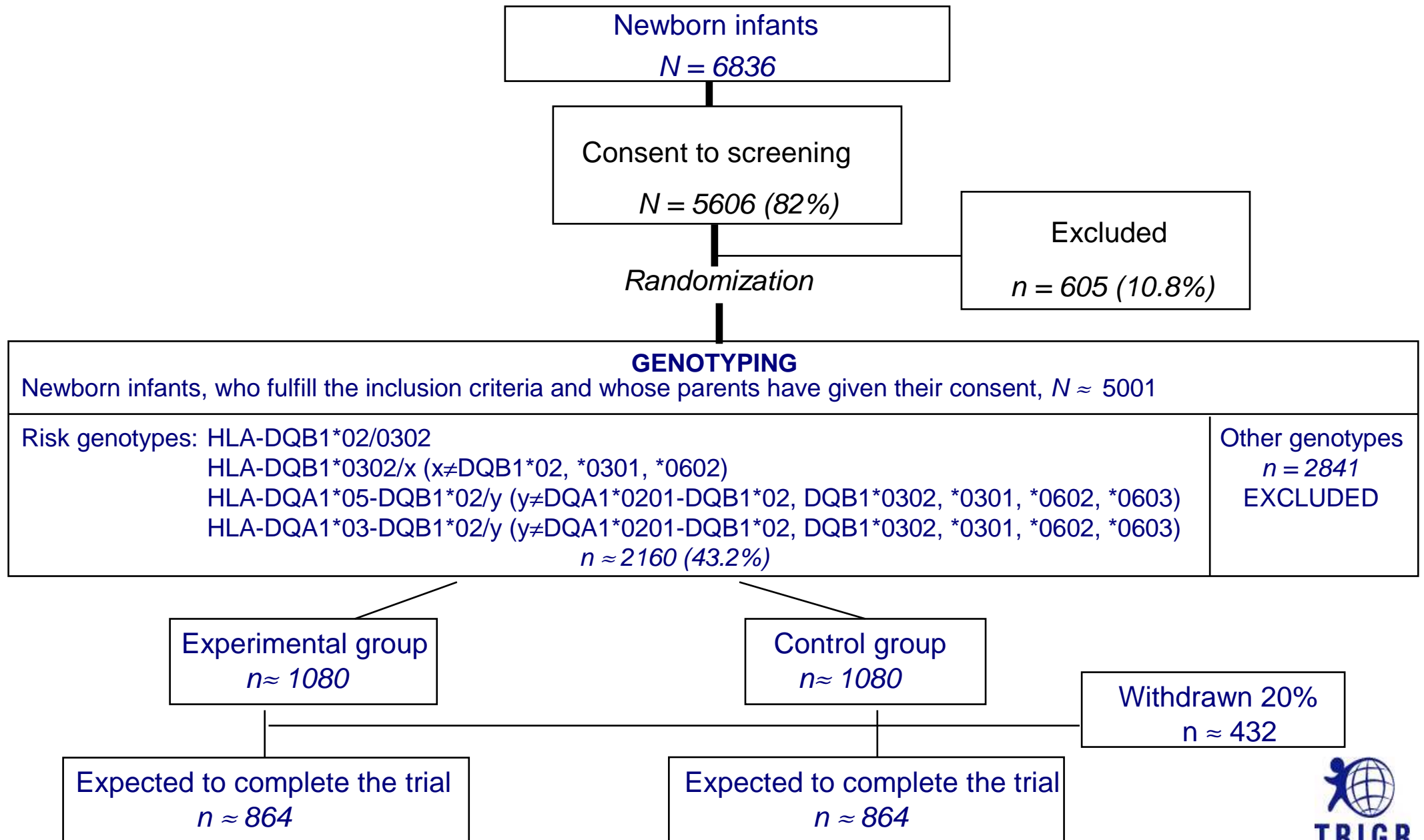
HLA DQB1*0302 and/or DQB1*0201

**Absence of HLA DQB1*0602,
DQB1*0603 or DQB1*0301**

PLANNING PARAMETERS FOR ESTIMATING SAMPLE SIZE NEEDED

- Alpha 5%
- Power 80%
- Drop-out rate 20%
- Adjustment for exclusive breast feeding up to the age of 6 months 10%
- Frequency of multiple (≥ 2) antibodies by the age of 6 years 9.9%
- Percent reduction in frequency of multiple antibodies 34.5%
- Frequency of type 1 diabetes by the age of 10 years 7.7%
- Percent reduction in frequency of type 1 diabetes 40%

FLOW SHEET FOR TRIGR





TRIGR Intervention I

- **All randomized subjects, before HLA results known**
 - **Breast milk**
 - **Study Formula**
 - **Nutramigen®**
 - **No other proprietary formula**

TRIGR Intervention II

- **6 Months**

Breast feeding at the discretion of the mother

Study formula when weaning

Casein hydrolysate (Nutramigen[®]) or intact cow's milk protein (Enfamil[®] + 20% Nutramigen[®])

No cow's milk protein in supplemental food

- **6-8 Months**

If the baby was exclusively breast-fed up to the age of 6 months, the mother was asked to add study formula to supplemental food and to avoid food containing cow's milk protein until the infant reached the age of 8 months



TRIGR Follow-Up

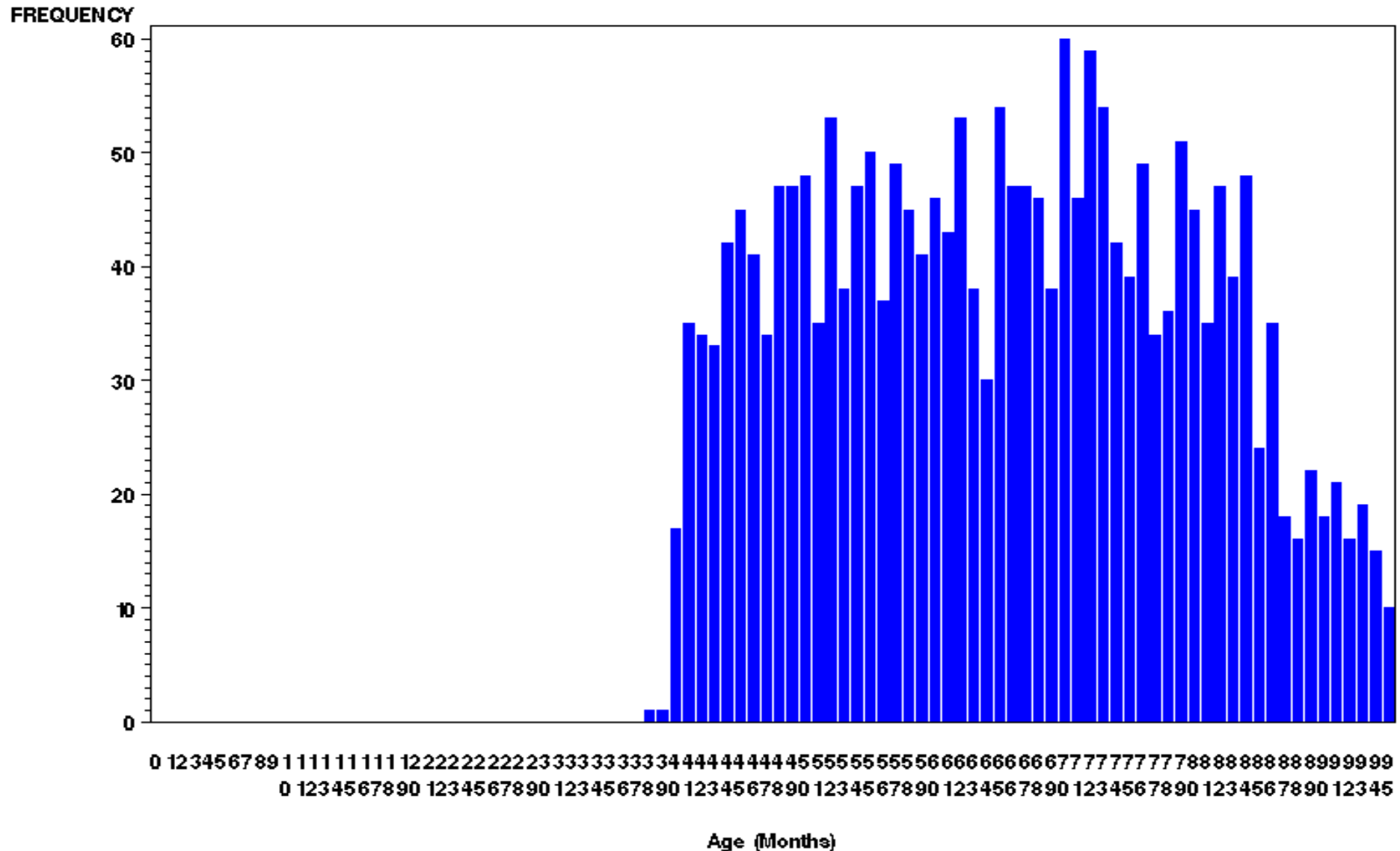
- **Visits at 3, 6, 9, 12, 18, 24 months and thereafter annually up to the age of 10 years**
- **Dietary records up the age of 9 months**
- **Compliance: cow's milk protein antibodies in cord blood and at 3, 6 and 9 months**
- **ICA, IAA, GADA, IA-2A in cord blood and at each visit**
- **OGTT at the age of 6 and 10 years**



PRESENT STATUS OF TRIGR

- 77 PARTICIPATING CENTERS FROM 15 COUNTRIES**
- THE RECRUITMENT WAS STARTED AT THE BEGINNING OF MAY, 2002, AND COMPLETED IN FEBRUARY 2007**
- 2160 RANDOMIZED PARTICIPANTS REMAINED IN THE STUDY AFTER HLA GENOTYPING. THE OLDEST CHILD HAS TURNED 8 YEARS AND THE YOUNGEST WILL BE 6-YEAR-OLD IN 02/2013 AND 10-YEAR-OLD IN 02/2017**

TRIGR Age Distribution of HLA Eligible Randomized Subjects by April 30, 2010





TRIGR: Expected outcome

Scenario 1: The intervention works →

First effective measure for primary prevention of type 1 diabetes → Recommendation that infants at increased genetic risk for type 1 diabetes should be weaned to a highly hydrolyzed formula



TRIGR: Expected outcome (cont'd)

Scenario 2: The intervention does not work →

Recommendation stating that weaning to a highly hydrolyzed formula does not decrease the risk of type 1 diabetes, and accordingly such formulas do not provide any benefits to infants at increased genetic susceptibility in terms of future risk for type 1 diabetes



FIRST ENDPOINT IN TRIGR PROPER WHEN APPLIED IN THE TRIGR PILOT

ENDPOINT: POSITIVITY FOR AT LEAST TWO AUTOANTIBODIES
AND/OR CLINICAL DIABETES

INTENTION TO TREAT ANALYSIS:

HAZARD RATIO 0.48 (95% CI 0.20-1.07; $P=0.073$)

*ANALYSIS ADJUSTED FOR THE GROUP DIFFERENCE IN EXPO-
SURE TO STUDY FORMULA:*

HAZARD RATIO 0.45 (95% CI 0.18-1.02; $P=0.055$)





WHY WOULD WEANING TO A HIGHLY HYDROLYZED FORMULA PROTECT AGAINST BETA-CELL AUTOIMMUNITY?

A highly hydrolyzed formula

- may decrease gut permeability
- may facilitate the maturation of regulatory T cells in the gut-associated lymphoid tissue (GALT)
- eliminates early exposure to intact bovine insulin
- may affect the gut microflora



ACHIEVEMENTS IN TRIGR

<i>Target</i>	<i>Achievement</i>
Recruitment of trial participants in 4 years	Completed in 4.3 years
Recruitment of 2032 eligible subjects	2160 (106%) recruited
Exclusive breastfeeding > 6 mo 10%	7.4%
Exposure to study formula > 80%	> 80%
Visit and form compliance > 80%	98%
Test compliance > 80%	94%
Lost-to-follow-up or non-participating subjects by the age of 10 years < 20%	10.9% by the mean age of 5.5 years



LESSONS FROM TRIGR

- International multicenter intervention trials in infancy aimed at weaning to a special infant formula are feasible
- Intervention trials looking for endpoints later in childhood or adulthood are major undertakings even when the intervention is implemented in infancy
- Rate of exclusive breastfeeding and of non-compliance with the intervention has to be taken into account in the sample size estimate for trials intervening with infant feeding
- An objective measure is desirable to monitor the compliance of the participants with the intervention



SUMMARY

- **Weaning to a highly hydrolyzed formula reduces the cumulative incidence of multiple autoantibody positivity with about 50% by the age of 10 years**
- **The full-scale TRIGR is well on its way and will provide a definite answer in year 2017 to the question whether weaning to a hydrolyzed formula will decrease the risk of clinical diabetes by at least 40% by the age of 10 years in children at increased risk for type 1 diabetes**



CONCLUSIONS

- **NUTRITIONAL INTERVENTION IN INFANCY MAY BE AN EFFECTIVE AND SAFE APPROACH FOR REDUCING THE SUBSEQUENT RISK OF TYPE 1 DIABETES**



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