Preventing Prematurity: Why New Discoveries are Needed to Decrease Infant Mortality

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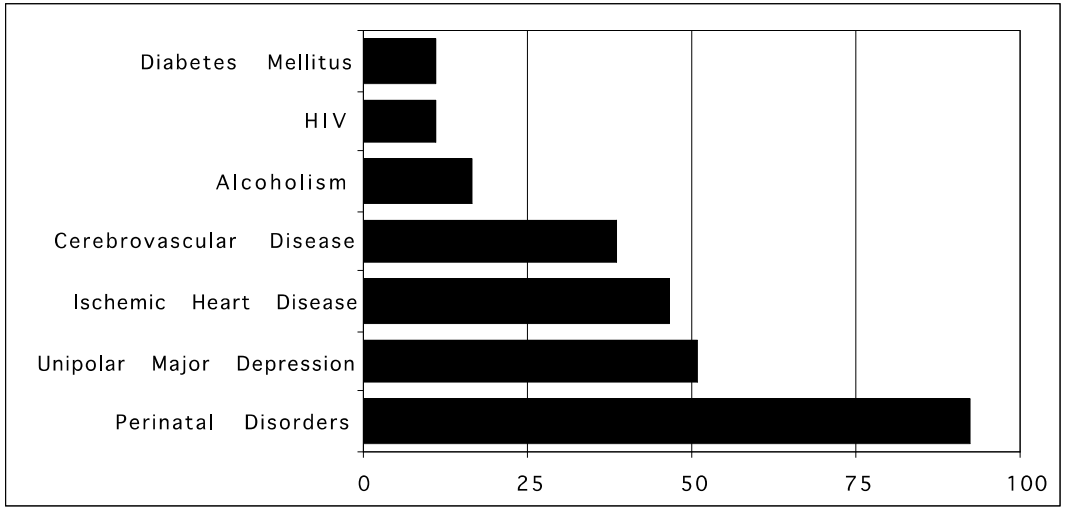
Preventing Prematurity - A Critical Unmet Need In Child Health

- Preterm birth (birth at less than 37 weeks of pregnancy) is a major public health concern worldwide.
- In Ohio, 10% of births occur before term.– preterm birth is the single largest cause of infant deaths.
- No generally effective interventions currently exist.



Worldwide Disability Adjusted Life Years (millions)

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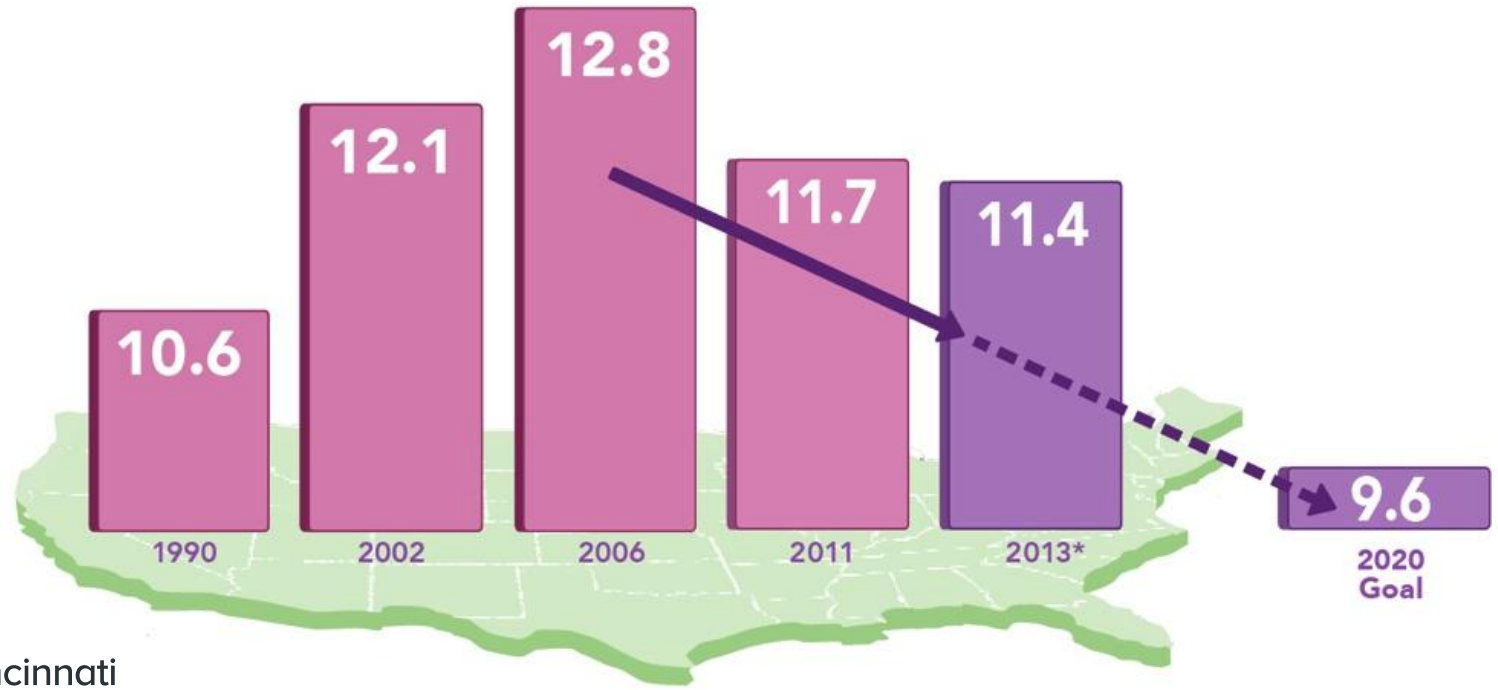
What Has Been Tried to Prevent Prematurity?

- More frequent visits for prenatal care
- Bed rest
- Risk reduction – such as smoking cessation
- Antibiotic treatment

- Elimination of Early Elective Deliveries
- Better management of fertility treatment
- Progesterone
- Cerclage (alone or with Progesterone)



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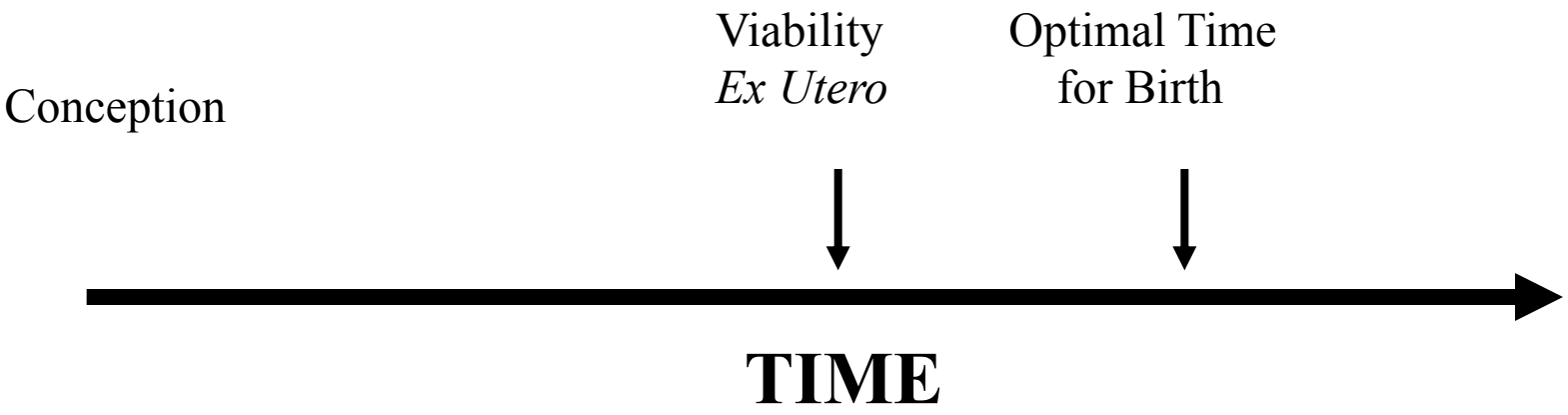
What determines the timing of birth?



Understanding preterm birth requires understanding the interplay between genetics, biology, environment, and key social determinants of health

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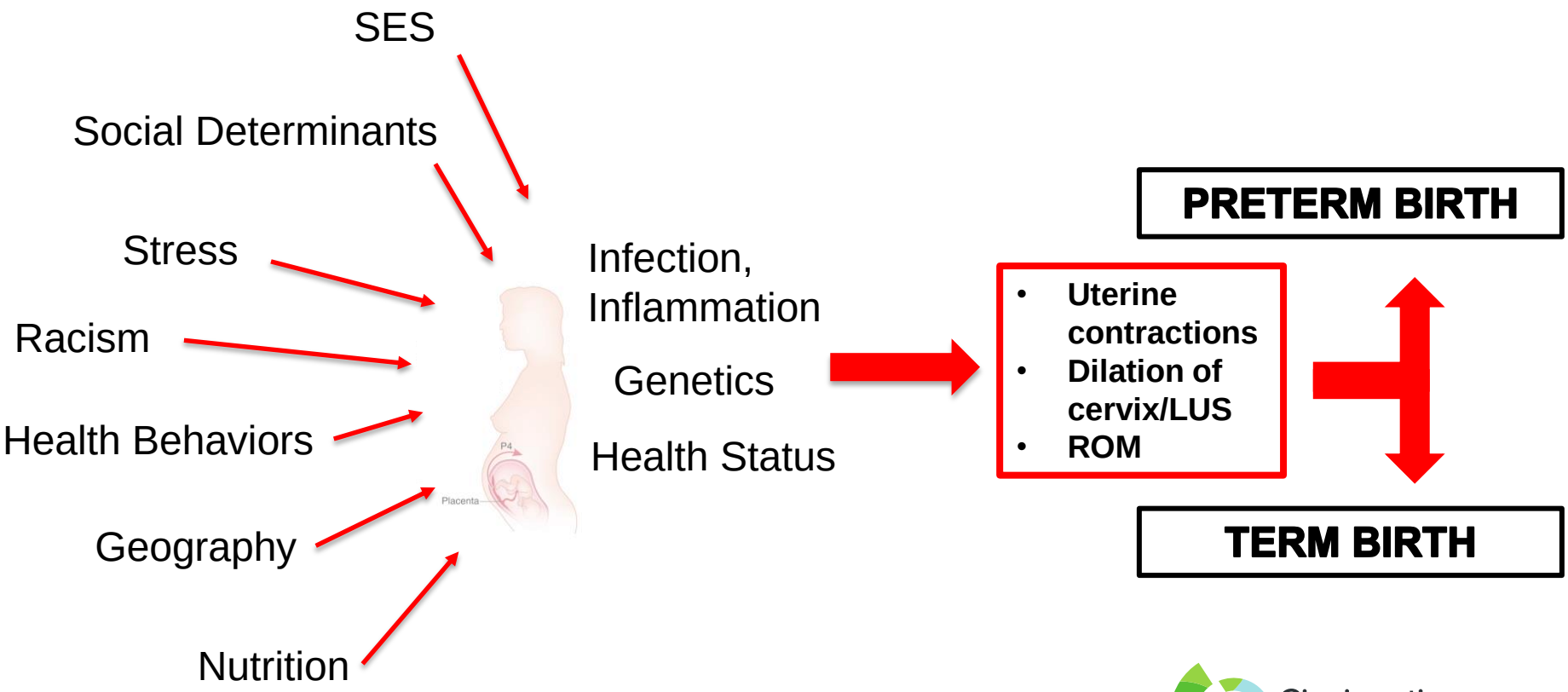
Many Factors Lead to Preterm Birth



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What possibilities would there be if genes contributing to preterm labor were identified?

- ***Prenatal identification*** of women at risk to allow close monitoring
- Identification of ***new therapeutic targets*** for treatment of active preterm labor
- ***Early detection*** of preterm labor before overtly active for early treatment institution
- Possible ***prophylactic therapy*** for all women (similar to folic acid for neural tube defects) –selenium as an example.

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Using Human Genetics to Unravel the Biology of Birth Timing and Prematurity

Hypotheses

Genetic variation in humans contributes to the risk of preterm birth

Identification of genes that predispose to preterm birth will provide new insight into normal mechanisms of control of parturition

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Why Consider Genetics?

- Sisters of women with preterm infants more likely to have preterm infants in studies from Scotland, Denmark and US
- Increased risk of delivering preterm infant if mother preterm
- 4-fold increase in recurrent preterm birth in African American mothers after adjustment for other risk factors

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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

ABSTRACT

BACKGROUND

Despite evidence that genetic factors contribute to the duration of gestation and the risk of preterm birth, robust associations with genetic variants have not been identified. We used large data sets that included the gestational duration to determine possible genetic associations.

METHODS

We performed a genomewide association study in a discovery set of samples obtained from 43,568 women of European ancestry using gestational duration as a continuous trait and term or preterm (<37 weeks) birth as a dichotomous outcome. We used samples from three Nordic data sets (involving a total of 8643 women) to test for replication of genomic loci that had significant genomewide association ($P<5.0\times10^{-8}$) or an association with suggestive significance ($P<1.0\times10^{-6}$) in the discovery set.

RESULTS

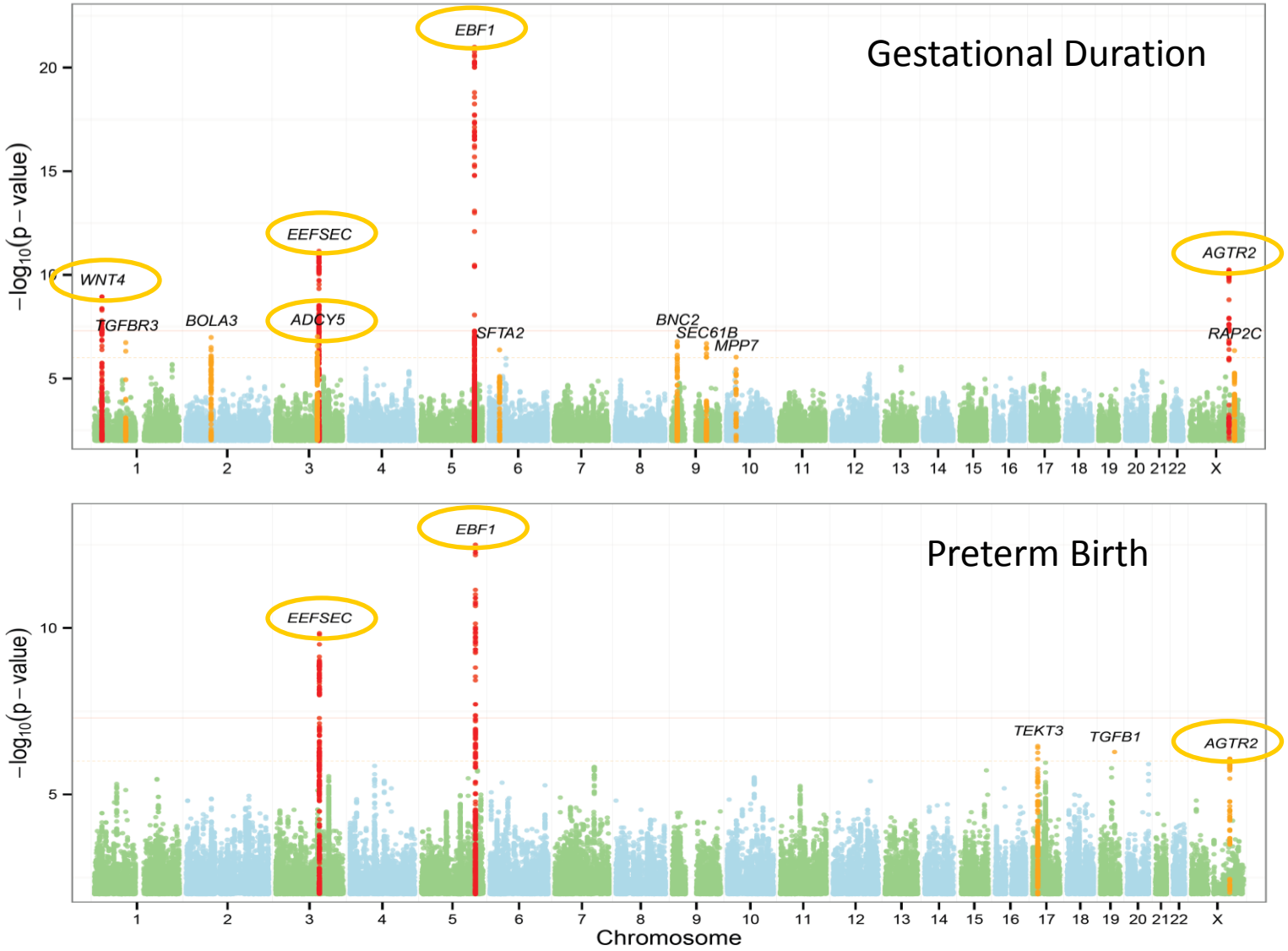
In the discovery and replication data sets, four loci (*EBF1*, *EEFSEC*, *AGTR2*, and *WNT4*) were significantly associated with gestational duration. Functional analysis showed that an implicated variant in *WNT4* alters the binding of the estrogen receptor. The association between variants in *ADCY5* and *RAP2C* and gestational duration had suggestive significance in the discovery set and significant evidence of association in the replication sets; these variants also showed genomewide significance in a joint analysis. Common variants in *EBF1*, *EEFSEC*, and *AGTR2* showed association with preterm birth with genomewide significance. An analysis of mother–infant dyads suggested that these variants act at the level of the maternal genome.

CONCLUSIONS

In this genomewide association study, we found that variants at the *EBF1*, *EEFSEC*, *AGTR2*, *WNT4*, *ADCY5*, and *RAP2C* loci were associated with gestational duration and variants at the *EBF1*, *EEFSEC*, and *AGTR2* loci with preterm birth. Previously established roles of these genes in uterine development, maternal nutrition, and vascular control support their mechanistic involvement. (Funded by the March of Dimes and others.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Muglia at Cincinnati Children's Hospital Medical Center, MLC 7009, 3333 Burnet Ave., Cincinnati, OH 45229-3026, or at louis.muglia@cchmc.org.

The first identification of maternal preterm birth genes revealed by Dr. Lou Muglia and colleagues at Cincinnati Children's



Zhang et al., NEJM 2017

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

New Targets for Intervention in Prematurity!

- Five Novel Genes: EBF1, WNT4, AGTR2, ADCY5, EEFSEC
- Selenium metabolism
- Does selenium deficiency predict preterm birth?

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March of Dimes Cross-Ohio Collaboration

Connecting Genetics with Social Determinants

Evidence

New Knowledge

Real People

cradle cincinnati
every baby, every day

MARCH OF DIMES
PREMATURITY RESEARCH CENTER
Ohio Collaborative

- Collective impact
- >28 partners
- Community engagement
- Service

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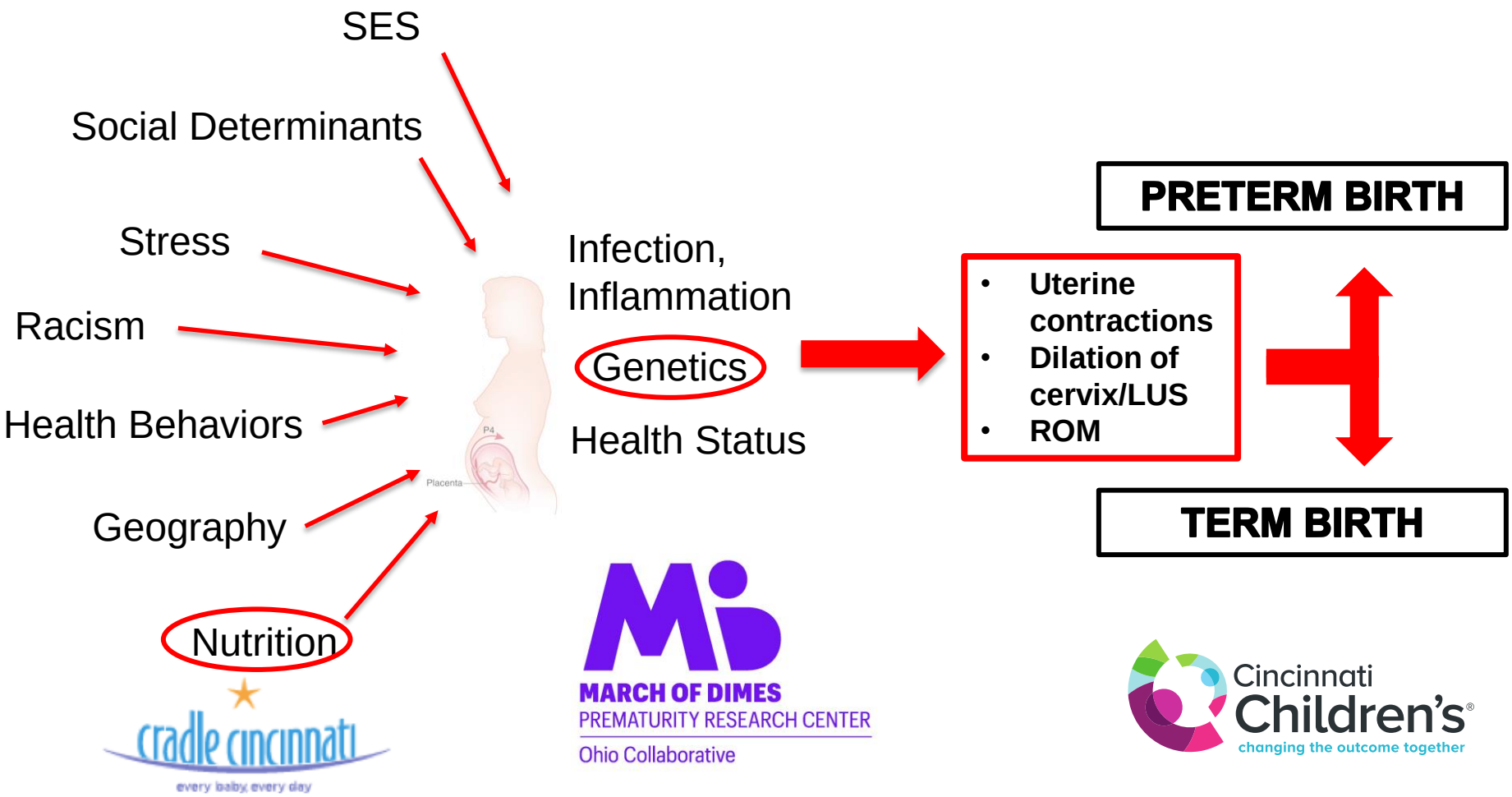
Many Factors Lead to Preterm Birth



Summary Concepts

- Prevention of preterm birth requires a comprehensive, integrated approach incorporating deep understanding of the social determinants of health AND the biological determinants of human birth
- The internationally recognized leaders in preterm birth research are right here in Ohio!

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