Preterm Birth

HuGENet Workshop

Atlanta, Georgia
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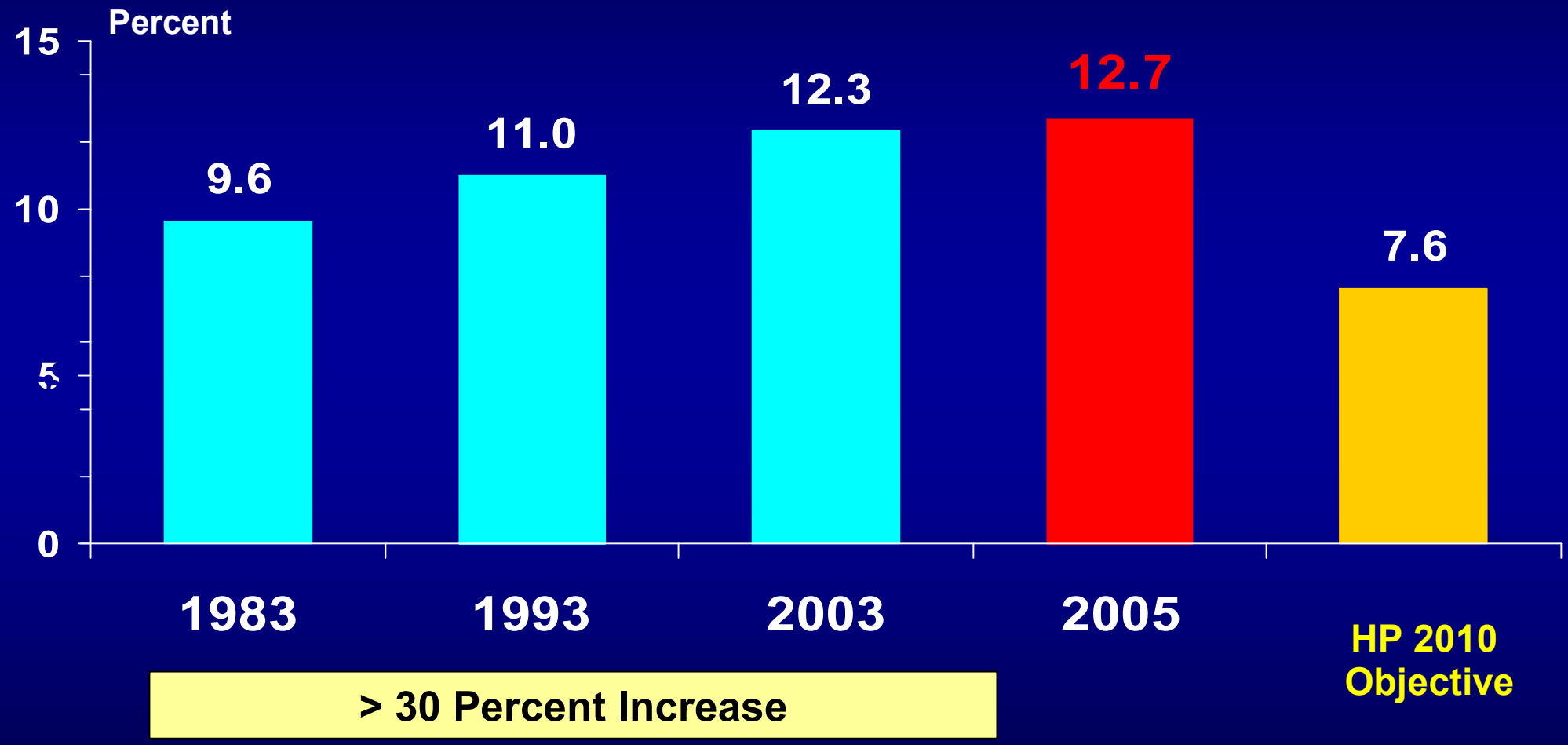
Preterm Birth (PTB) is a MAJOR public health challenge, with lifelong consequences including childhood illness as well as predisposition to adult disease.

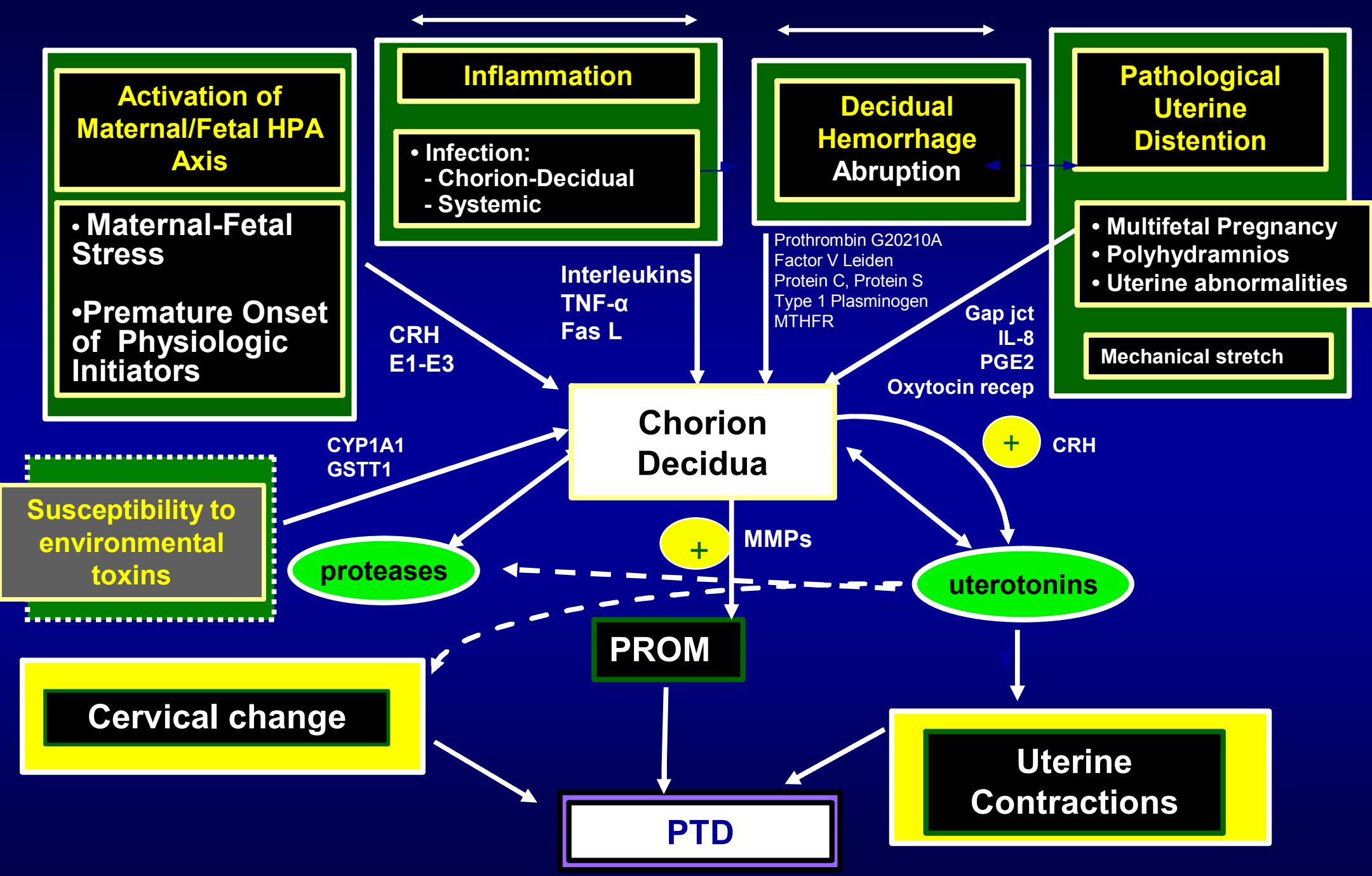
There are few->no effective prediction or prevention strategies for PTB.

Preterm Birth Rates
United States, 1983, 1993, 2003, 2005



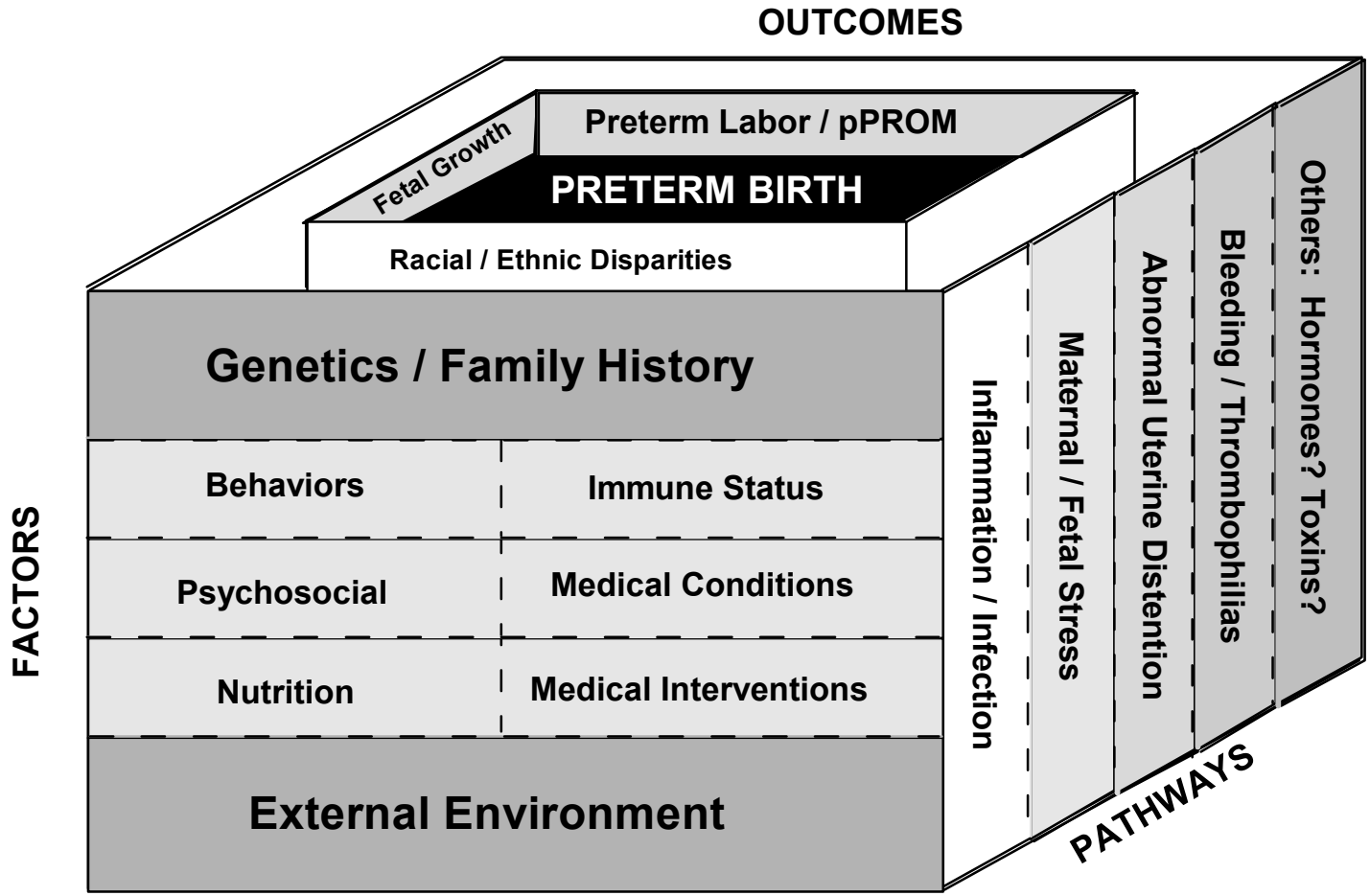
Preterm is less than 37 completed weeks gestation.
Source: National Center for Health Statistics, final natality data
Prepared by March of Dimes Perinatal Data Center, 2005

March of Dimes
Saving babies, together



Adapted from: C. J. Lockwood, E. Kuczynski, *Paediatr Perinat Epidemiol* **15**, 78 (2001) & X. Wang et al. *Paediatr Perinat Epidemiol* **15**, 63 (2001)

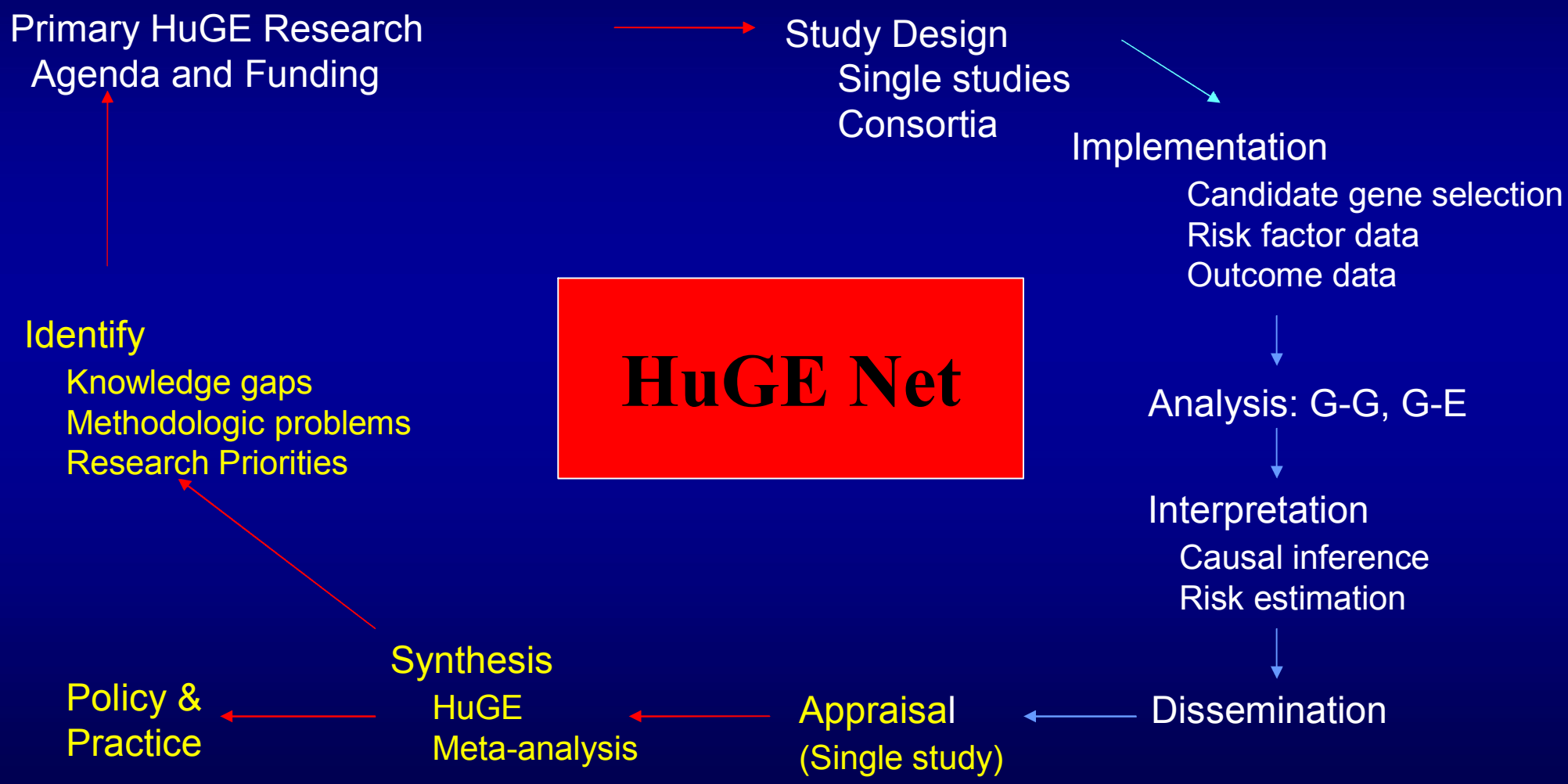
Research Agenda for Preterm Birth: Recommendations from the March of Dimes



AJOG (2005) 193, 626-635

How can we summarize what we know and what we don't know about gene disease association in preterm birth?

From HuGE Research to Synthesis & Dissemination for Policy and Practice



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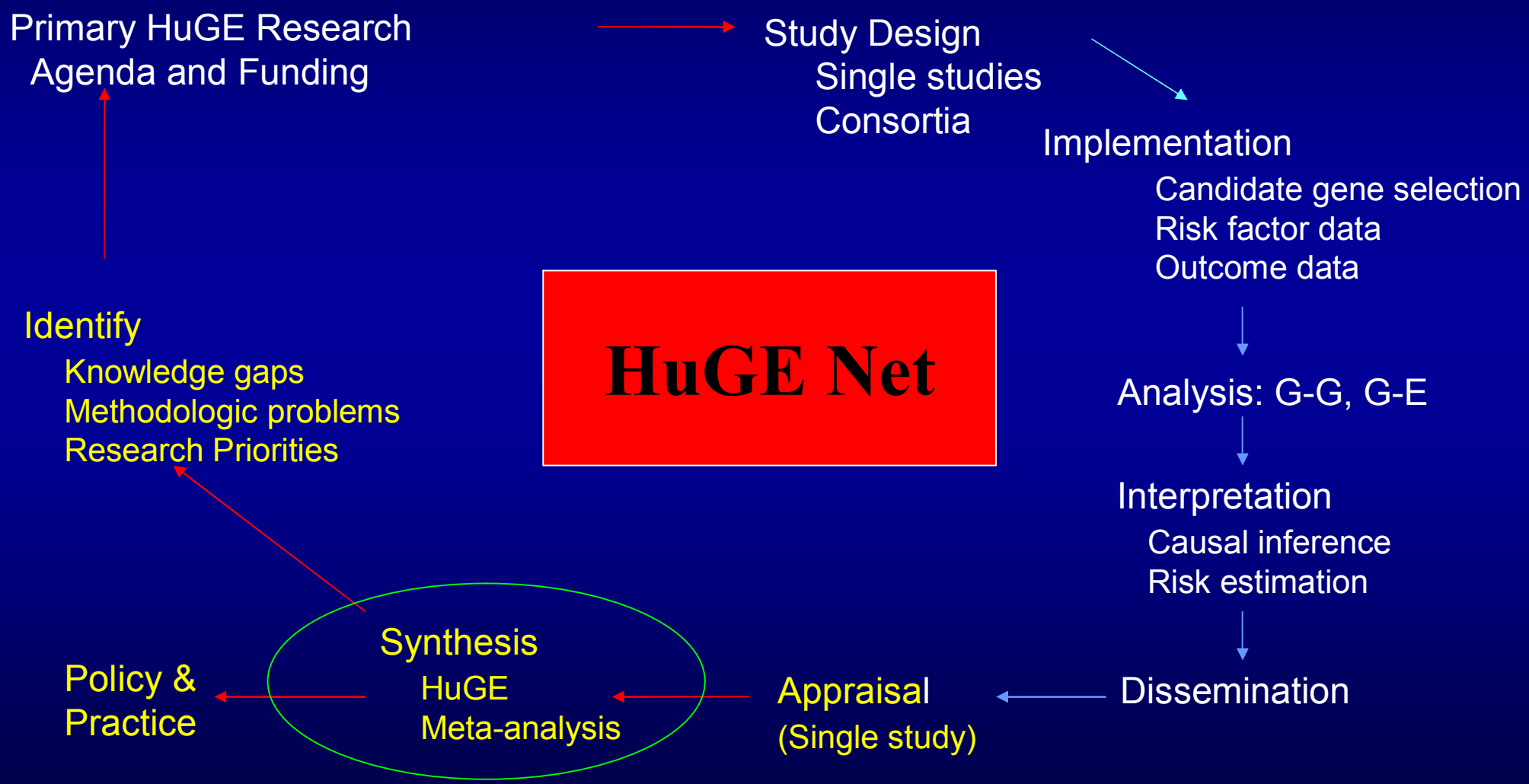

What would a snapshot synopsis of the field of genetics and preterm birth look like?

Systematic Review and Meta-Analysis: Gene Disease Association in Preterm Birth

Preterm Birth International Collaborative (PREBIC) Working Group

Tomas Allen, WHO
Ana Pilar Betran, WHO
Siobhan Dolan, AECOM
Judith Eckardt, Medical Student
Mads Hallegard, Statens Serum Institut
Bruce Lin, MOD
Ram Menon, Nashville
Mario Merialdi, WHO
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PUBMED and EMBASE Search Strategy

PUBMED (Medline) and EMBASE – to cover the world literature

Search run covering 1/1/1990 – 4/12/2007

Identified 5421 abstracts

Followed up with additional search covering 4/12/07 – 1/2/08

Identified 561 abstracts

PUBMED and EMBASE Search Strategy

Step	Search query	Number of abstracts
1	((("Pregnancy Complications"[MeSH]) OR pregnancy/) AND ((premat*) OR (pre-matur*) OR (preterm*) OR (pre-term*) OR (prematurity) OR ("premature birth"))) AND (("genetic polymorphisms" OR "genetic polymorphism") OR ("Genetic Phenomena"[MeSH]) OR ("genetic polymorphism"[Text Word] OR "polymorphism, genetic"[MeSH Terms]) OR ("gene polymorphism*") OR (ge[All Fields]) OR (("genetic diseases, inborn"[MeSH Terms] OR "genetic predisposition to disease"[MeSH Terms] OR "predisposition"[Title/Abstract] OR "susceptibility"[Title/Abstract] OR "defect"[Title/Abstract] OR "defects"[Title/Abstract]) OR ("genetics"[MeSH Terms] OR "genetic processes"[MeSH Terms] OR "genetic phenomena"[MeSH Terms] OR "genetic structures"[MeSH Terms] OR "genotype phenotype"[Title/Abstract] OR "somatic"[Title/Abstract] OR "germline"[Title/Abstract])) OR (haplotype[TIAB] OR haplotypes[TIAB] OR haplotyping[TIAB] OR allele[TIAB] OR alleles[TIAB] OR allelic[TIAB] OR phenotype[TIAB] OR phenotypes[TIAB] OR genetic[TIAB] OR genetics[TIAB] OR genomic[TIAB] OR genomics[TIAB] OR gene[TIAB] OR genes[TIAB] OR heterozygote[TIAB] OR heterozygotes[TIAB] OR heterozygous[TIAB] OR homozygote[TIAB] OR homozygotes[TIAB] OR homozygous[TIAB] OR mutation[TIAB] OR mutations[TIAB] OR somatic[TIAB] OR soma[TIAB] OR hereditary[TIAB] OR heritable[TIAB] OR germline[TIAB] OR germ[TIAB] OR inherit[TIAB] OR inherits[TIAB] OR inherited[TIAB] OR kin[TIAB] OR kinship[TIAB] OR kindred[TIAB]))	
2	limit 1 to (humans and publication yr=1990 - 2007)	5421

Process

- We retrieved the full copy PDF of each article identified
- We pulled the citations and loaded them into a shared RefMan database
- We collaborated with Lars Bertram of Alzheimer Research Forum and using his EXCEL template, extracted genotype data from all articles that met inclusion criteria:
  - 46 articles reporting data on
  - 55 genes
  - 100 SNPs
- Meta-analysis is currently underway

Final Results

	Abstracts	Full Text Review	Included in Analysis
1st search ('90-4/12/07)	5421	91	42
2nd search (4/12/07-2/1/08)	561	20	4
Totals	5982	111	46

Screening Abstracts (n=5982) -> Full Text Review (n=111)

Manual human process, undertaken by 2 reviewers, using inclusion and exclusion criteria.

FIRM Inclusion Criteria
Human

LIKELY Inclusion Criteria
1) Must give case description to include:
    a) gestational weeks at delivery (continuous variable) or status as preterm versus term with definition of preterm (<32 weeks, <37 weeks, or otherwise defined)
    b) phenotypic description which might be abstracted as:
        1) PTB – indicated spontaneous
        2) PTB – PPROM
        3) PTB – twins
        4) PTB – medical conditions (preeclampsia, diabetes, etc)
        5) PTB – SGA & IUGR
2) study design
    a) # cases and controls
    b) case only
3) measure of association (OR or RR) and CI or p value with outcome of PTB
4) genotype data
    a) maternal?
    b) fetal?
    c) paternal?
5) Geographic location where study took place
6) Race/ethnicity/ancestry of study population
    a) how was race/ethnicity determined?
    b) was the analysis pooled or stratified?
7) Single study versus meta-analysis

Full Text Review (n=111) -> Inclusion in Analysis (n=46)

- Articles were excluded because:
  - Did not provide genotype data (n=11)
  - Reported allele frequency only (n=4)

Full Text Review (n=111) -> Inclusion in Analysis (n=46)

- **Articles were excluded because:**
  - Did not study PTB as an outcome (n=16)
  - Outcomes studied included:
    - PPROM, Low Birthweight, Chorioamnionitis, Cystic Fibrosis, Bronchopulmonary dysplasia, Retinopathy of Prematurity, etc.

Full Text Review (n=111) -> Inclusion in Analysis (n=46)

- Articles were excluded because:
  - Review articles (n=6)
  - mRNA or protein expression studies (n=4)
  - Case only / case reports (n=6)

Very Preliminary Findings

Meta-analysis required 4 or more samples

- **18 genes, 43 SNPs are being analyzed**

Very preliminary findings:

PON1 – paraoxanase 1 **(bind reversibly to organophosphate substances)**

PON2 – paraoxanase 2

Gene	Polymorph	Model	Stratum	OR	upper 95% CI	lower 95% CI	P-value	# Samples
PON1	rs662	random	ALL	0.87189	0.99273	0.76576	0.03843	4
PON1	rs662	random	CAU	0.85719	0.99889	0.7356	0.04836	4
PON1	rs662	random	EXCL_INITIAL	0.89263	1.02276	0.77906	0.10187	4
PON2	rs12026	random	ALL	1.21012	2.35123	0.62282	0.57357	4
PON2	rs12026	random	EXCL_INITIAL	1.64096	2.26796	1.1873	0.0027	4
PON2	rs7493	random	ALL	0.54122	0.74044	0.3956	0.00012	4
PON2	rs7493	random	EXCL_INITIAL	0.56253	0.85683	0.36931	0.00737	4

Challenges

- Phenotype: What is preterm birth?

- NCHS defines preterm birth as birth before 37 completed weeks gestation, but authors defined it in varying ways:
  - < 37 weeks (n=29)
  - < 36 weeks (n=4)
  - < 35 weeks (n=7)
  - < 34 weeks (n=3)
  - < 32 weeks (n=2)
  - < 27 weeks (n=1)

Challenges

- Etiology creeps into the definition of phenotype
  - Is the PTB due to chorioamnionitis? Twins?
- Preterm Birth represents a complex heterogeneous phenotype.
  - Not all studies give a comprehensive clinical description of the phenotype.
  - Is all PTB the same?
- Preterm birth has historically been mixed with low birthweight, and that legacy continues to confuse the literature

Challenges

- Inconsistency in reporting the major and minor allele …. Which is which?
- Reporting was all over the map.
- Many studies do not include rs numbers, although recent studies are reporting them more routinely.

- We solved this by using the Ancestral Allele in dbSNP as the major and the variant as the minor.

Challenges

- Baseline genotype data not always given
- Heterozygotes and homozygous minor allele combined in reporting (often because study is small)
- Only allele frequency data reported
- Genotype data presented in obscure formats

Challenges

- Multiple Genomes – maternal and fetal genotypes reported, and very occasionally paternal
- Should they be combined? … looked at separately?
- Family-based studies vs. case control studies
- Methodological challenge remains

Challenges

- Plenty of PTB is iatrogenic, caused by:
  - Malpractice
  - Imperative to intervene
  - Desire to act on behalf of the fetus and mother
  - Unrealistic public perception
    - PTB is not such a big deal
    - Elective cesarean on maternal request is gaining acceptance
    - Convenience and planning play a role in delivery
- None of this will be explained by genetic factors

Challenges

- Few large cohorts exist, leading to challenges in identifying replication cohorts.

Grading the Evidence

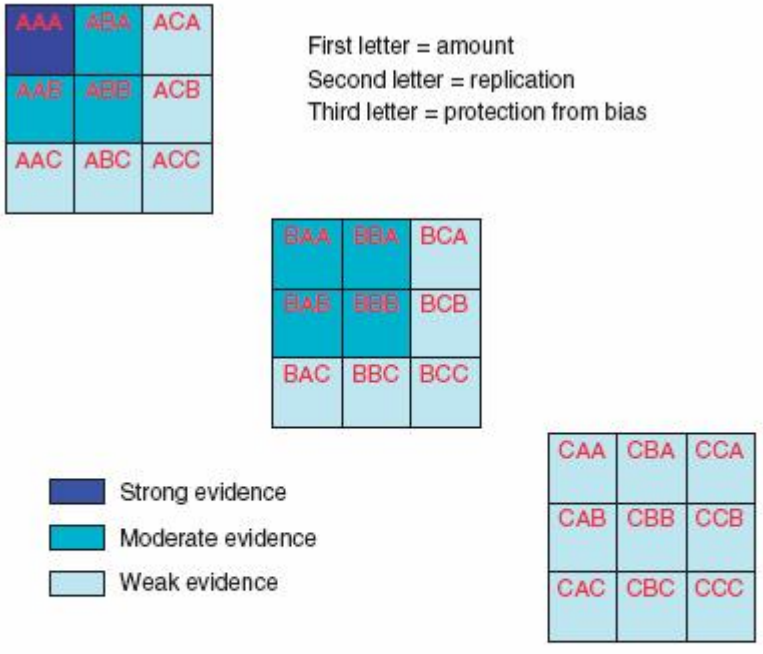


Figure 1 Categories for the credibility of cumulative epidemiological evidence. The three letters correspond (in order) to amount of evidence, replication and protection from bias. Evidence is categorized as strong, when there is A for all three items, and is categorized as weak when there is a C for any of the three items. All other combinations are categorized as moderate

Ioannidis et al. IJE 2007

Amount of evidence

A. Large scale evidence
   - > 1000 subjects (total # cases and controls assuming 1:1 ratio) evaluated in the least common genetic group of interest

B. Moderate amount of evidence
   - 100 – 1000 subjects in this group

C. Little evidence
   - < 100 subjects in this group

Replication

A. Extensive replication including at least one well-conducted meta-analysis with little between-study inconsistency

B. Well-conducted meta-analysis with some methodological limitations or moderate between-study inconsistency

C. No association, no independent replication, failed replication, scattered studies, flawed meta-analysis, or large inconsistency

Protection from Bias

A. Bias, if at all present, could affect the magnitude but probably not the presence of the association

B. No obvious bias that may affect the presence of the association, but there is considerable missing information on the generation and accumulation of evidence

C. Clear presence of bias that can affect even the presence or not of the association

Grading the Evidence

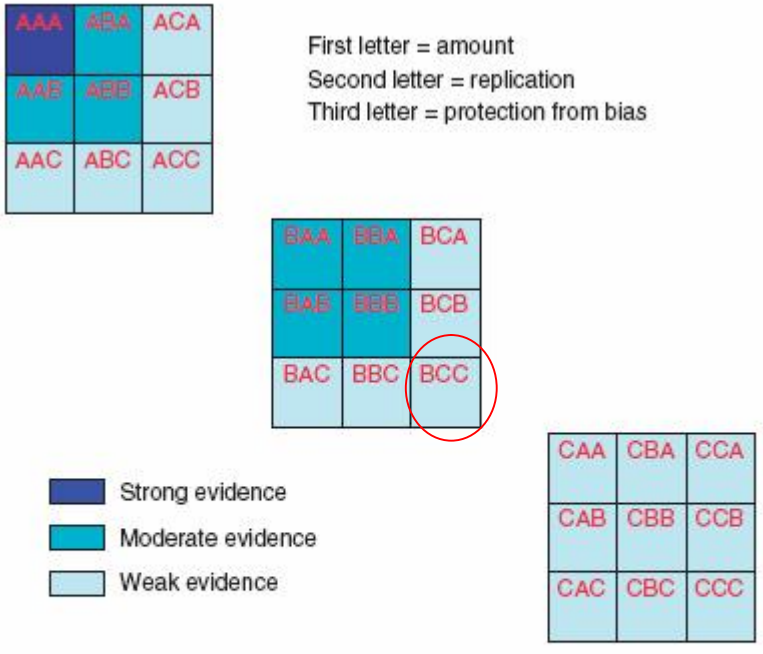


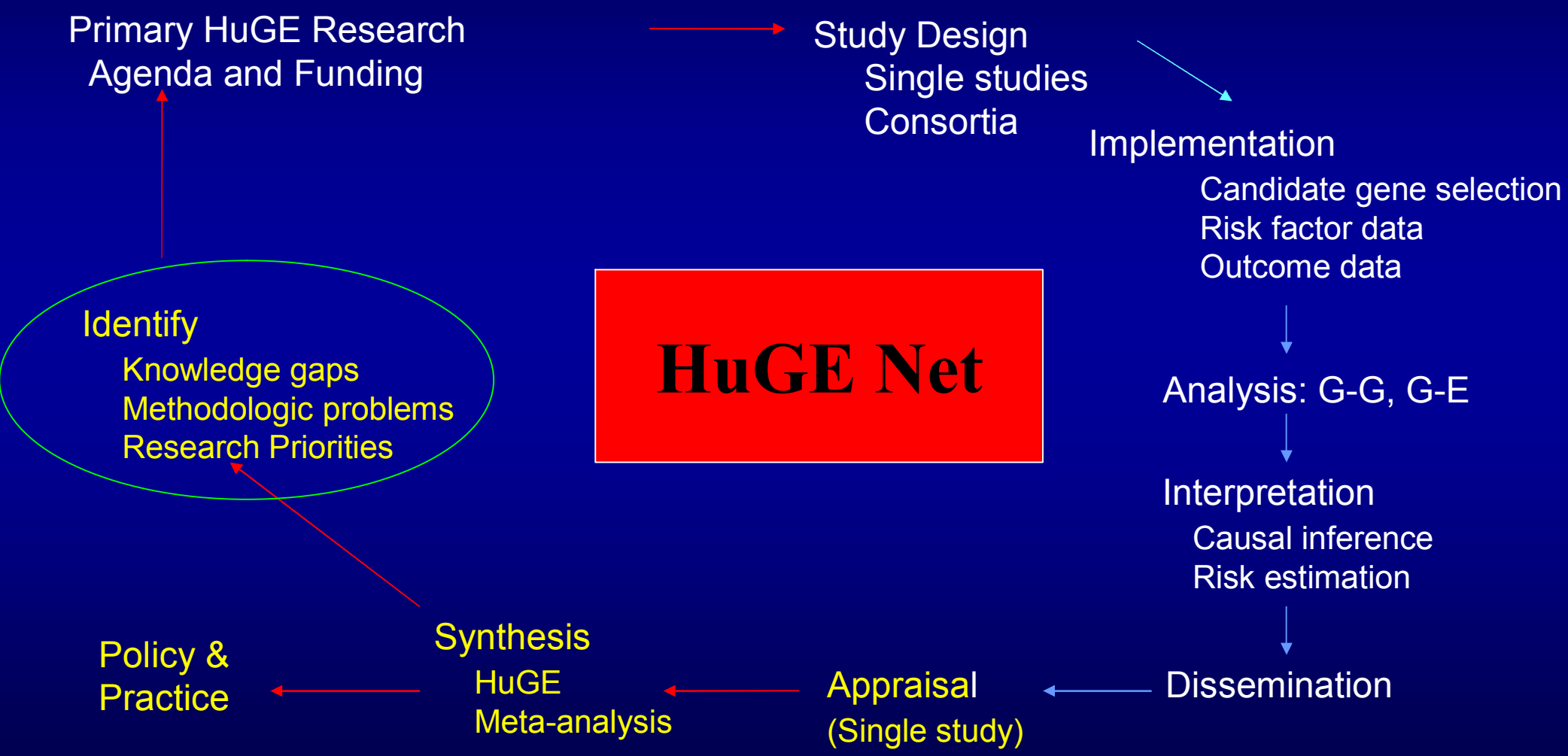
Figure 1 Categories for the credibility of cumulative epidemiological evidence. The three letters correspond (in order) to amount of evidence, replication and protection from bias. Evidence is categorized as strong, when there is A for all three items, and is categorized as weak when there is a C for any of the three items. All other combinations are categorized as moderate

Ioannidis et al. IJE 2007

Summary

- The public health burden of preterm birth warrants greater research efforts.
- Consortia are being formed, but more are needed to allow rapid replication of findings.
- Global standards would be valuable as they would facilitate meta-analysis as well as guide interested researchers and clinicians who are doing the primary research and have very little perspective on the big picture!

From HuGE Research to Synthesis & Dissemination for Policy and Practice



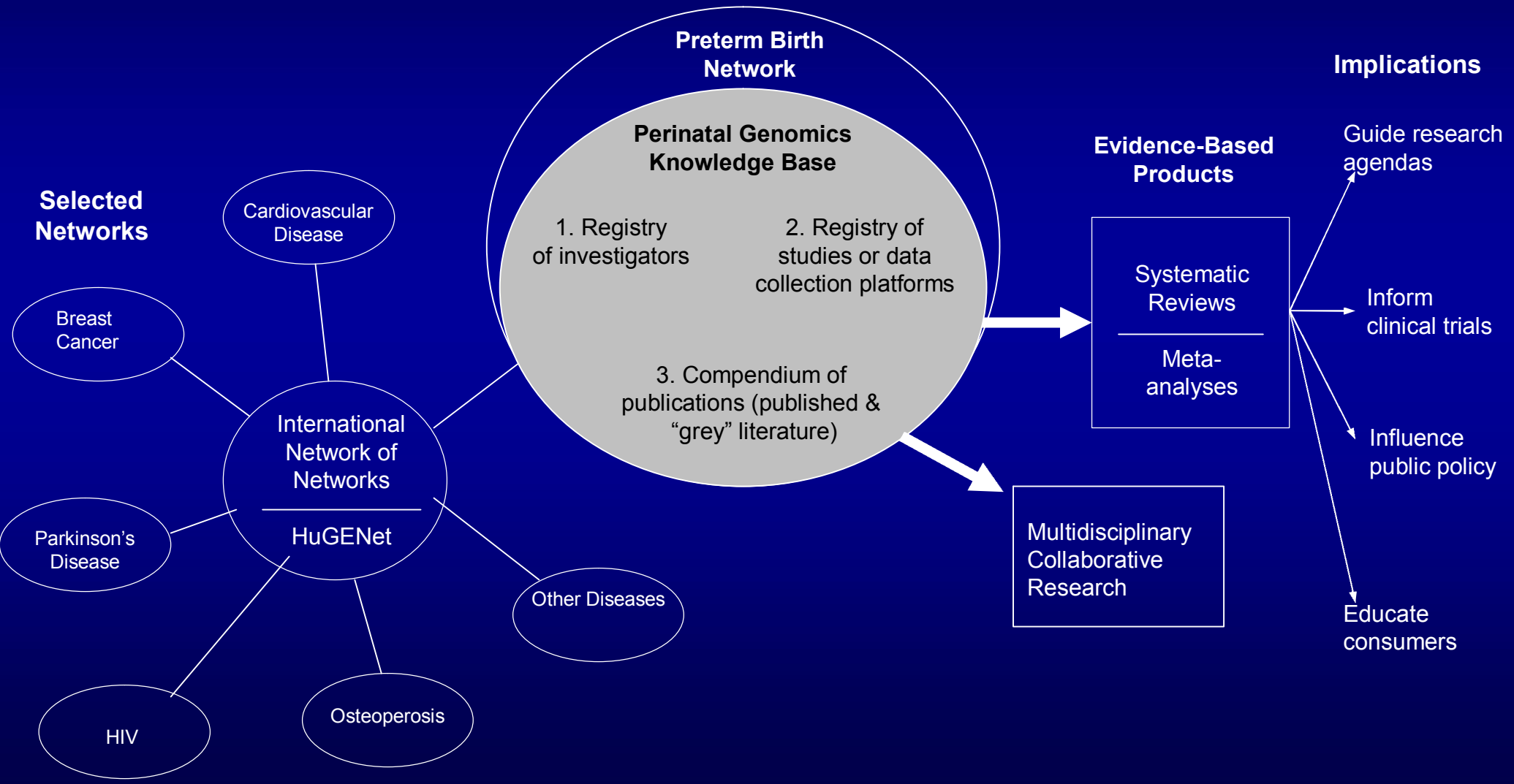
Summary

- Recommendation: Plain vanilla genotype data should be presented in all gene-disease association studies – a standardized “Table 2” which provides the 2x3 table of genotypes for each race/ethnicity.
- GWAS will likely be insightful, as new ideas are needed.

PREBIC Consortium Next Steps

- Write up findings for publication
- This will become the basis for the dynamic online knowledge base which is being developed in conjunction with Wei Yu at CDC.
- PREBIC Consortium submitted a grant for a GWAS in Fall 2007.
- Continue to serve as a pilot for HuGE Net

Perinatal Genomics: A Knowledge Base for Genetics and Prematurity



Thank You!

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