



Genetic Ecosystem Across the Lifespan

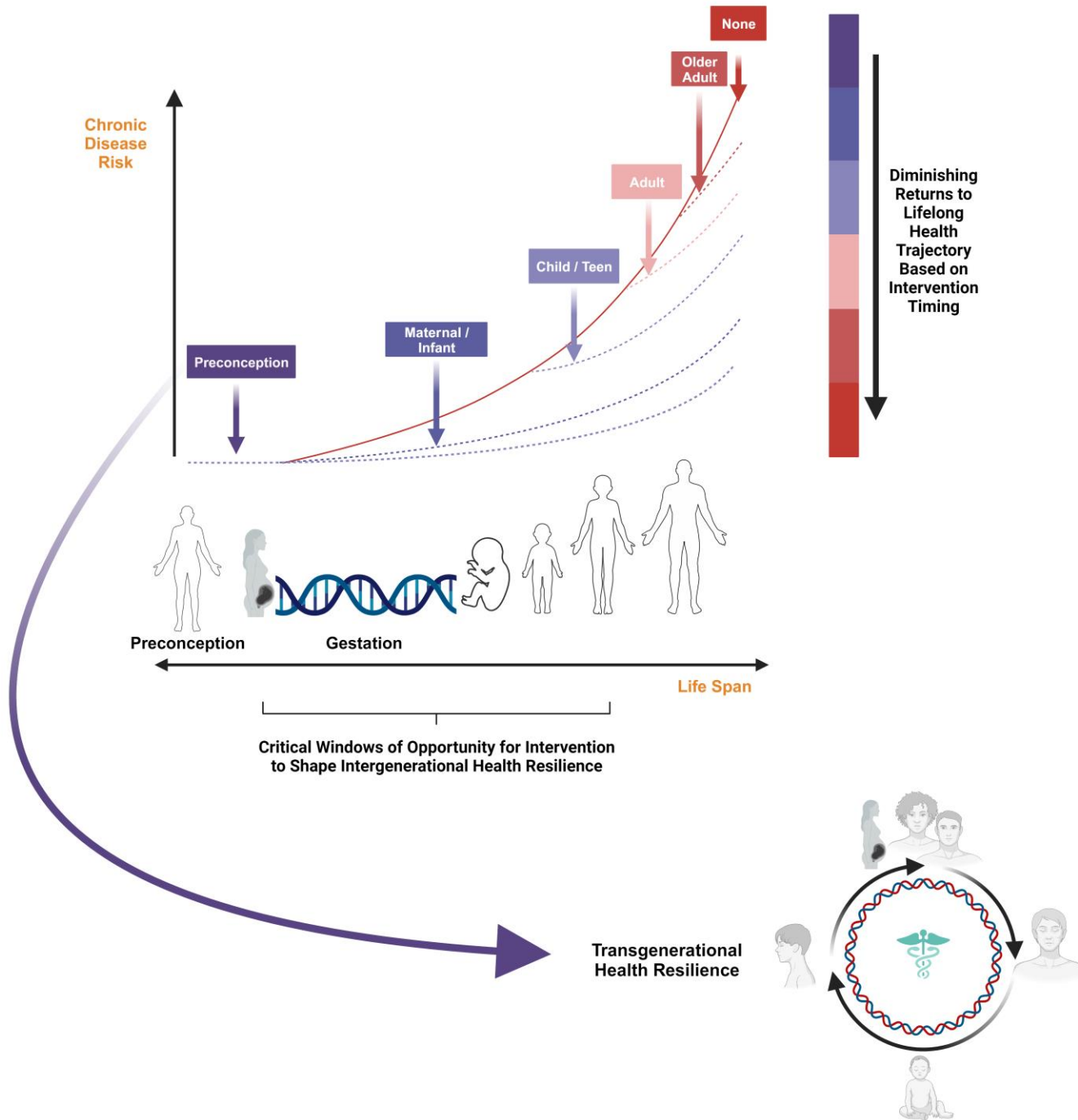
Leslie Stone MD, FP/OB Fellow, IFMCP

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Transgenerational

- ✓ Opportunity
- ✓ Impact
- ✓ Resilience

...Revolution!





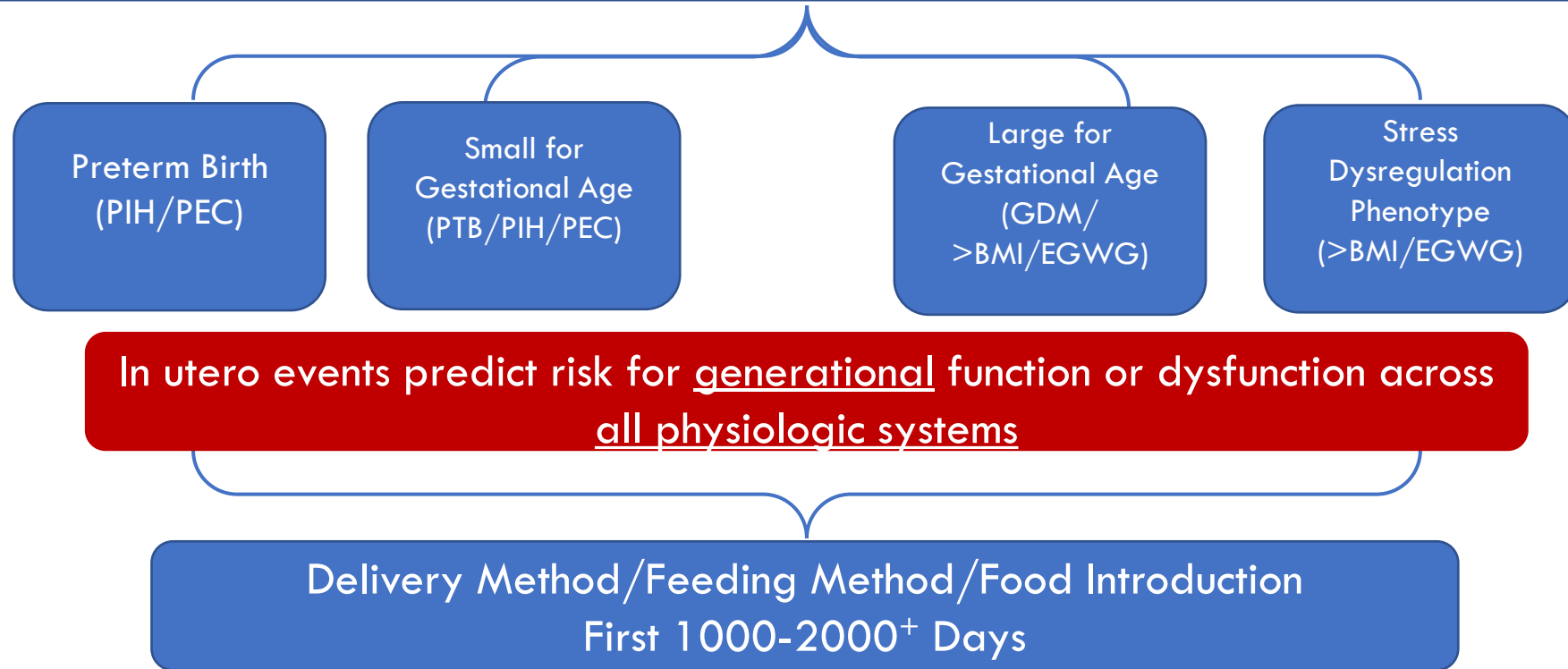
Preconception

- **Recognize:** Modifiable nutrition/lifestyle factors contributing to health
- **Empower:** Change
- **Goal:** Optimization of preventative care for all men & women of reproductive age...
 - ✓ 49% of pregnancies are unintended¹
 - ✓ 16.7% of pregnant women begin care in 2nd trimester (after organogenesis)²
 - ✓ NO traditional preconception care for men

1. Finer LB et al. *Contraception*. 2011;84(5):478-485.

2. CDC. National Vital Statistics Reports. Timing and Adequacy of prenatal care in the United States, 2016.

Developmental Programming of Health & Disease (DOHaD)



PIH: Pregnancy Induced Hypertension/PEC: Preeclampsia/PTB: Preterm Birth/GDM: Gestational Diabetes Mellitus/BMI: Body Mass Index/EGWG: Excessive Gestational Weight Gain

Preterm Birth

7.9% & increasing...

- AMA
- increased IVF
- Multifactorial

Leading cause of neonatal death = complications of PTB

Long term: HTN, cardiac dysfunction, (chronic) obstructive pulmonary disorder (COPD), increased blood glucose, increased mental health disorders including ADHD, increased PTB in subsequent generations.





Small for Gestational Age (SGA)

2.6% in 2020 increasing to 2.9% in 2021 across all regions

Associated with highest short & long-term health vulnerability across the lifespan

Short-term: Lower verbal, spatial, and numerical test scores in childhood.

Long-term: Dyslipidemias, hypertension, unfavorable body fat distribution, non-insulin dependent diabetes mellitus.

Large for Gestational Age (LGA)

23.8%

Maternal Obesity (avg. 31%) is a stronger predictor of an LGA infant than maternal hyperglycemia.

Long-term: predictor of obesity in adulthood, higher risk of hypertension, type 2 diabetes mellitus (T2DM), cardiovascular disease, and certain forms of cancer later in life





Gestational Diabetes Mellitus (GDM)

5% - 20+% (?)

Screening challenges - a $\frac{1}{4}$ of high-risk women - not screened for GDM or received little or no clinical management after diagnosis.

Short-Term: GDM assoc. with four-fold increased risk of late stillbirth.

Long-Term: Approximately $\frac{1}{2}$ of all women with a history of GDM go on to develop T2DM within five to ten years after delivery. A previous diagnosis of GDM carries a lifetime risk of progression to T2DM of up to 60%.

National Pregnancy in Diabetes Audit 2021 & 2022, for England and Wales, Hospital and Community Health Services, Hospital Trusts, NHS Trusts, published 12 Oct 2023.

International Diabetes Federation, UK 10th Ed. 2021 –Diabetes Report 2000-2045

<https://diabetesatlas.org/data/en/country/209/gb.html>

UK Health Security Agency - <https://ukhsa.blog.gov.uk/2021/03/04/patterns-and-trends-in-excess-weight-among-adults-in-england/> - Caroline Hancock, Posted on: 4 March 2021

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Hypertensive Disorders of Pregnancy (HDP)

Preeclampsia – 3.5%

4X increased death rate in 2022 compared to 2020.

HDP - up to 10% of pregnancies

Short & Long-term Outcomes:

Increased rate of maternal morbidities - seizures, stroke, kidney injury, increased SGA and PTB <34 weeks, and increased perinatal deaths



Nutrients Commonly Depleted/Inadequate Intake

...with **Developmental Consequences**

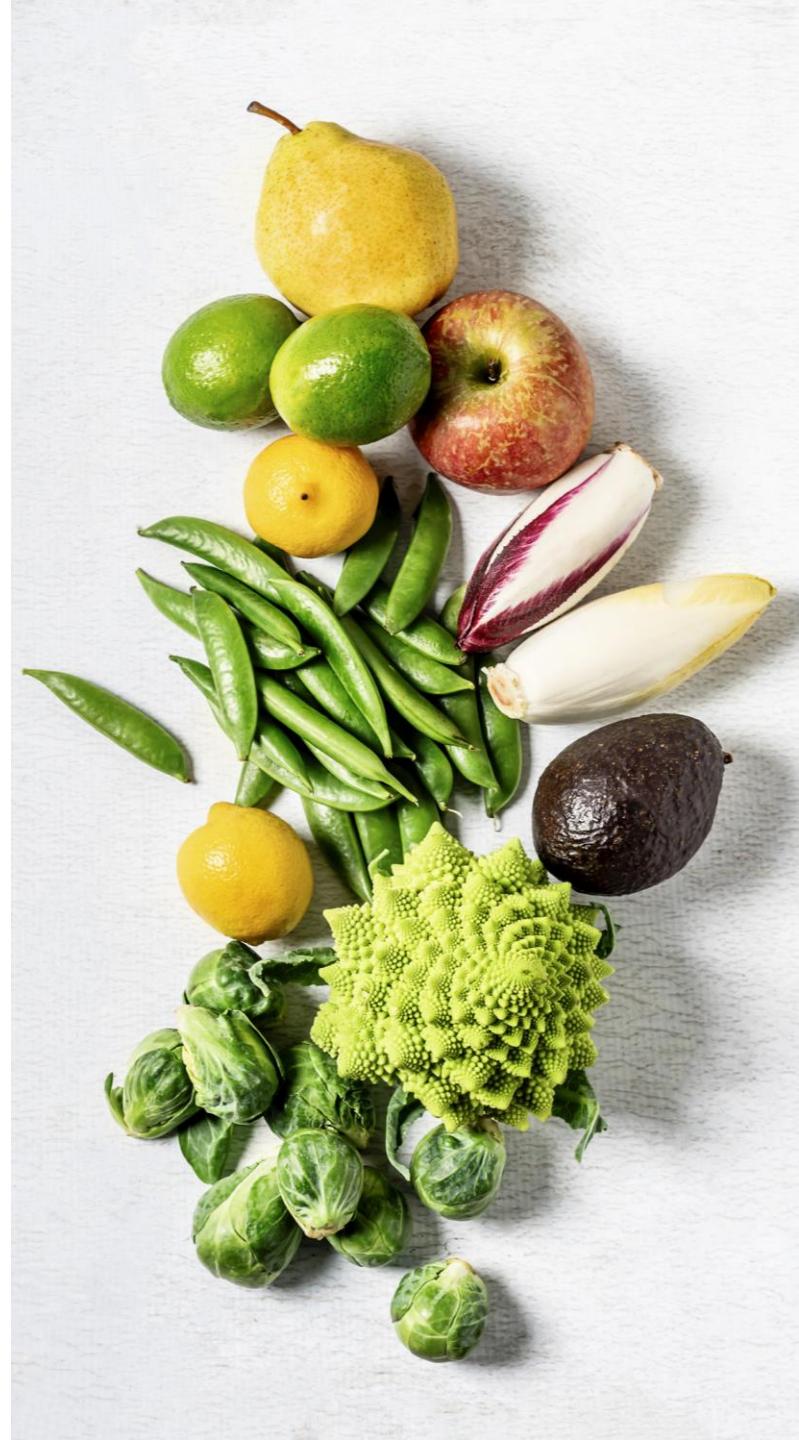
Vitamins: Riboflavin, Niacin, Pyridoxyl-5-phosphate, Folate, Cobalamin, Choline, Betaine

Minerals: Magnesium, Zinc, Calcium, Iron

Fats: Omega-3 fatty acids

Amino Acids: Methionine, cysteine

Phytochemicals: Genistein, sulforaphane, resveratrol





DOHaD
&
Common
Nutrient
Deficiencies

- **25-OH D deficiency:** ↑ risk of GDM, ↑ risk of LGA, ↑ risk of F1 DMII
- **Carnitine deficiency:** ↑ risk of GDM, ↑ risk of LGA
- **Zinc deficiency:** ↑ risk of PTB, ↑ risk of SGA, ↓ risk of F1 neural function
- **Iron deficiency:** ↑ risk of SGA
- **EFA deficiency:** ↑ risk of PTB, ↓ F1 brain weight
- **Lack of microbiome diversity:** ↑ F1 asthma, allergy, atopy
- **Maternal protein calorie deficiency:** ↑ risk of SGA

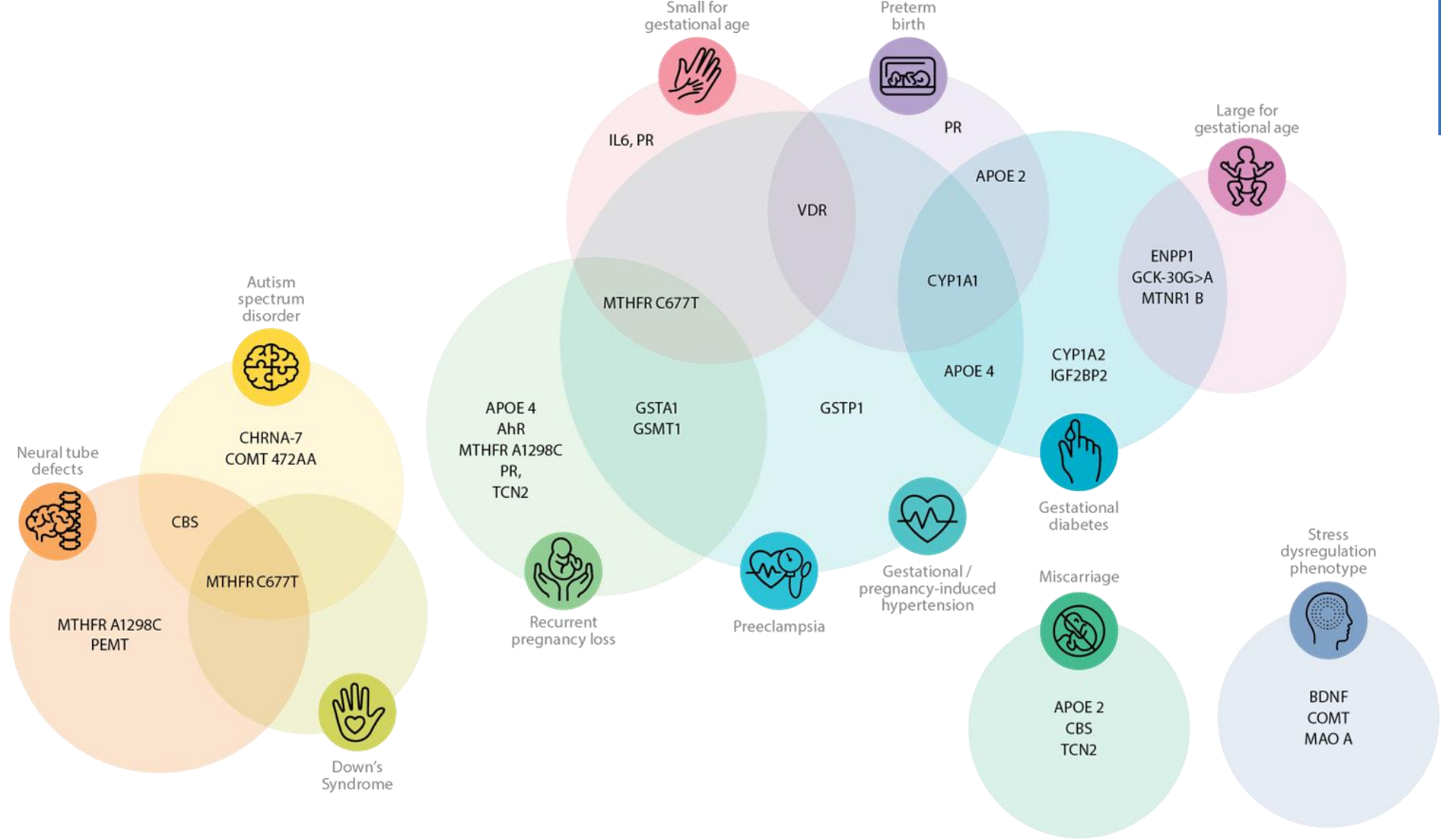
References listed on slide 38

Phenotype Condition Outcome



- ✓ **Overlap**
- ✓ **Interplay**
- ✓ **Opportunity**

42 SNPs in 27 genes involved in 11 key biological processes associated with preconception outcomes, as well as maternal and fetal health outcomes.



Genetic Ecosystem Across the Lifespan



Mother

Baby



MTHFR C677T

RPL
Preeclampsia
Small for Gestational Age

MTHFR A1298C

RPL
NTD

TCN2

RPL
Miscarriage

VDR

Preterm Birth
Small for Gestational Age
Gestational HTN

MTNR1B

GDM

APO e2

Miscarriage
Preterm Birth
GDM

MTHFR C677T

NTD
ASD
Down's syndrome
Vascular dementia
Stroke
Some CA
Schizophrenia*
T2DM
Male Infertility

MTHFR A1298C

Male infertility
Some CA
Protective for Hypothyroid

* African, Asian, Caucasian
** European descent

TCN2

Failure to thrive
Substance misuse
B12 cellular delivery
Infertility
Recurrent Implantation failure
Crohn's disease
Hyper-homocystinemia**

VDR

Asthma
HTN
>BFP
OA
Osteoporosis
Vitamin D deficiency
Squamous/Basal Cell cancer
Melanoma

MTNR1B

T2DM
Childhood-Obesity risk
Adulthood-Obesity traits
Chronotype-
Breast CA
Colorectal CA

APO e2

Protective for Alzheimer's
Hyper-Lipoproteinemia
T2DM





Select Nutrient & Gene Variant Analysis in a Targeted Diet & Lifestyle Analysis & Preterm Birth (SNGLI-PTB)

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Clinical Trials ID NCT 05436119





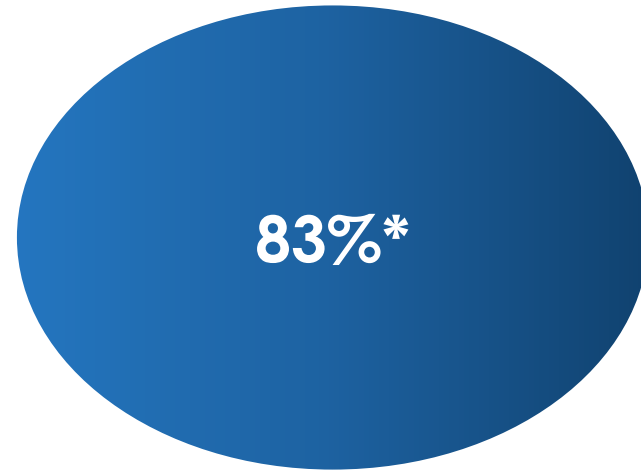
Background & Purpose

1. **Reverse** rising maternal & neonatal adverse outcomes
2. **Target** populations at greatest risk
3. **Reduce** medical economic impact
4. **Build Resilience**

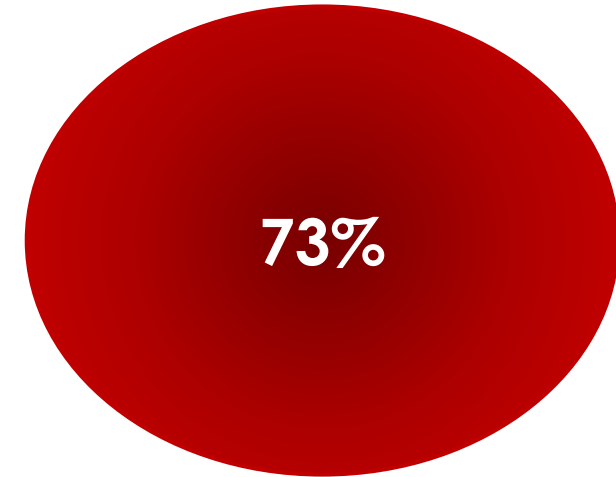
Diverse & High-Risk – OB Medicaid Population

Ethnicity

- Black
- Hispanic
- Asian



High Risk Pregnancies



*Compared to MACPAC US data where 61% Medicaid beneficiaries are BIPOC.

Nutrient Deficiencies – 2nd/3rd Trimester Labs

Vitamin D:
100%
Insufficient

Zinc:
44%

Carnitine:
67%






Iron:
17%

DHA-DBS
Suboptimal
89%

DHA
Breastmilk
100%*

*4 of 15 patient samples collected

Genotype Trends

BIOLOGICAL AREA	SNP	GENOTYPE CALL	FREQUENCY
 Methylation	MTHFR C677T	Risk allele(s) present	39%
	MTHFR A1298C	Risk allele(s) present	44%
	MTHFR A1298C & C677T	Risk allele present	11%
 Vitamin B12 transport	TCN2	Risk allele present	61%
 Melatonin receptor	MTNR1B C>G	Risk allele present	44%
	MTNR1B C>T	Risk allele present	50%
	MTNR1B C>G & MTNR1B C>T	Risk allele present	39%
 Insulin secretion	SLC30A8 G>A	Risk allele present	94%
 Vitamin D metabolism	VDR FokI T>C	Risk allele present	44%
	VDR C>T	Risk allele present	56%
	VDR A>G	Risk allele present	89%
	VDR FokI T>C, C>T & A>G	2x risk alleles present	67%
	VDR FokI T>C, C>T & A>G	3x risk alleles present	11%

Standard of Care Vs. Standard of Care^{Plus}

- ⚡ Reactionary
- ⚡ Intervention Only
- ⚡ Population-Based
- ⚡ Worsening Outcomes
- ⚡ Increasing Costs



- ✓ Revolutionary
- ✓ Prevention + Intervention
- ✓ Personalized & Precise
- ✓ Highly Effective
- ✓ Highly Cost Efficient
- ✓ Profound
Transgenerational Impact



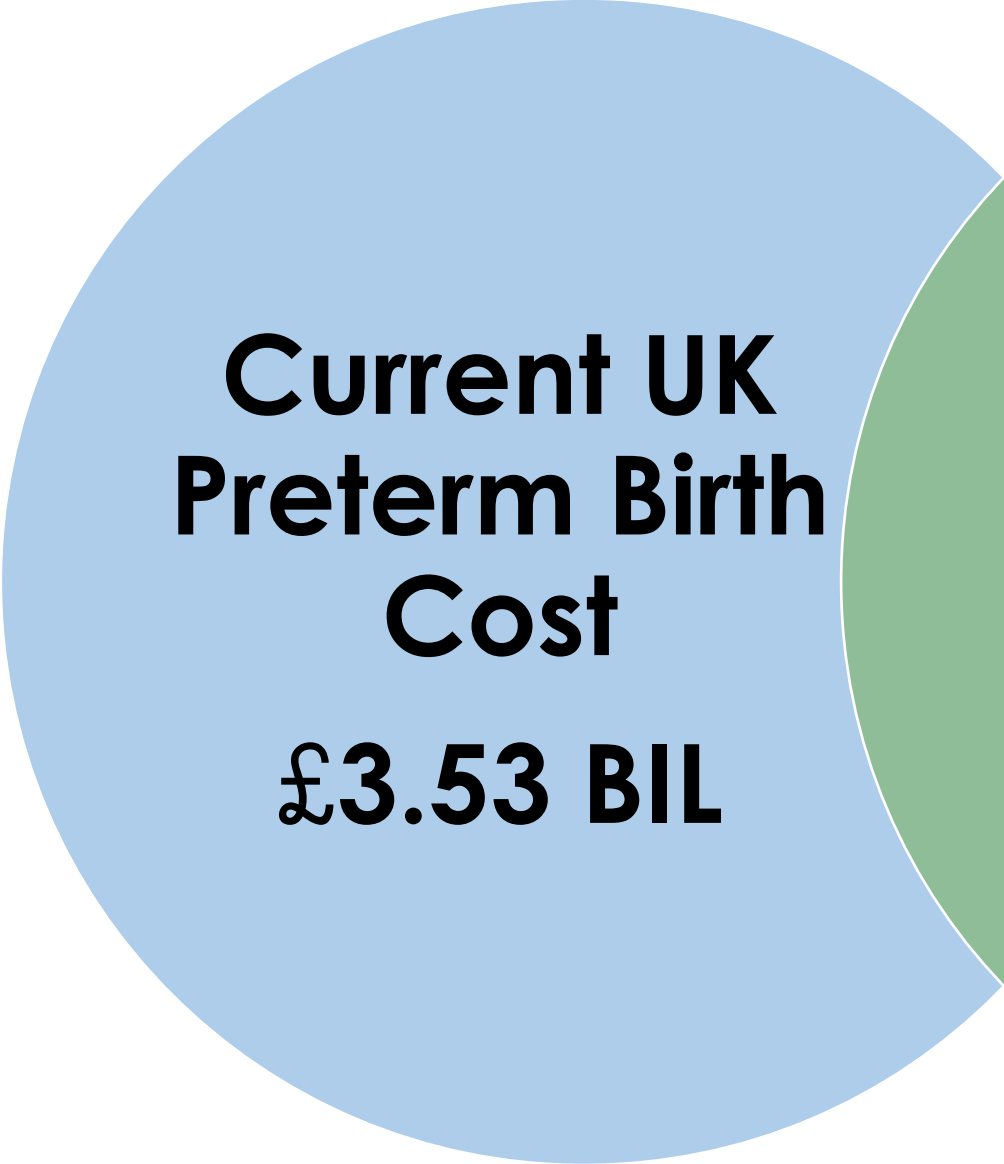
Outcome	GrowBaby® UK Impact*	Long-term health associations - decreasing the risk for generations
<i>Preterm Birth (PTB)</i>	4X less likely	Perinatal mortality, long-term morbidity, developmental issues, coronary heart disease in males, elevated blood pressure in females, & atherogenic lipids in males, F1 generation PTB recurrence.
<i>Small for Gestational Age (SGA)</i>	2X less likely	Dyslipidemias, hypertension, unfavorable body fat distribution, non-insulin dependent diabetes mellitus & lower verbal, spatial, and numerical test scores in childhood.
<i>Hypertensive Disorders of Pregnancy (HDP)</i>	10X less likely (HDP) & 21X less likely (PEC)	Increased rate of maternal morbidities: seizures, stroke, kidney injury, increased SGA and PTB <34 weeks, and increased perinatal deaths. 14% of all maternal deaths are from pregnancy-induced hypertension. Rates of chronic hypertension two to five years after affected pregnancies are 50% following early-onset preeclampsia, 39% following gestational hypertension, and 25% following late onset preeclampsia.
<i>Gestational Diabetes Mellitus (GDM)</i>	10X-41X less likely	Maternal type 2 diabetes (T2DM) & possible adverse cardiometabolic outcomes in the offspring. Approximately half of women with a history of GDM go on to develop T2DM within five to ten years after delivery. A previous diagnosis of GDM carries a lifetime risk of progression to T2DM of up to 60%.
<i>Large for Gestational Age (LGA)</i>	6X less likely	Being born LGA is a predictor of obesity in adulthood. High birth weight (LGA) is also associated with higher risk of hypertension, type 2 diabetes mellitus (T2DM), cardiovascular disease, and certain forms of cancer later in life.



UK GrowBaby® Savings Model

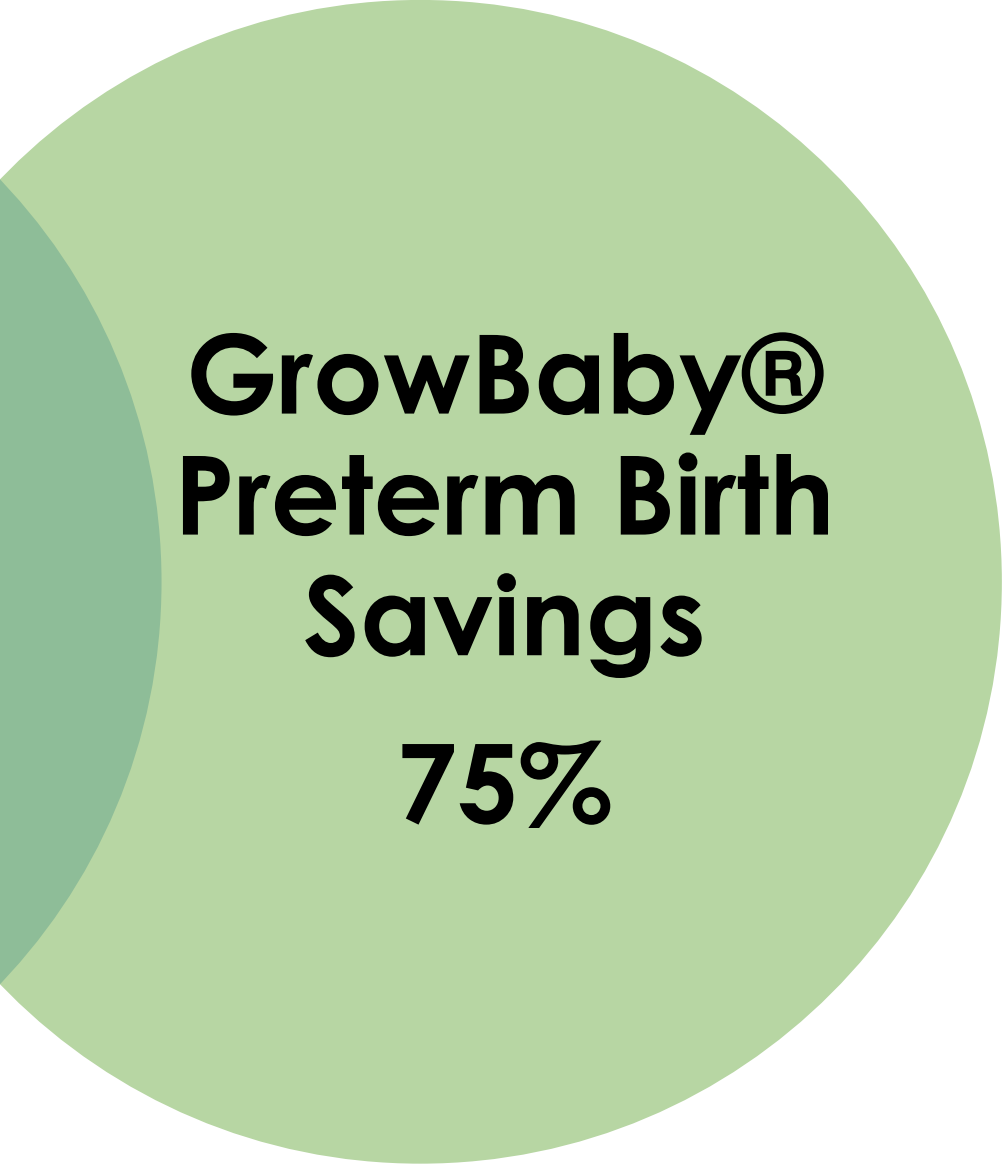
Outcomes	Current UK Cost/Annum	Savings with GrowBaby® /Annum
Preterm Birth	£3.53 BIL	£2.64 BIL
Small for Gestational Age	£49 MIL	£24 MIL
Gestational Diabetes Mellitus	£201 MIL-£804 MIL	£181 MIL - £784 MIL
TOTAL:	£3.78 BIL-£4.38 BIL	£2.84 BIL - £3.44 BIL

Reliable GBP (£) cost per outcome is scarce for HDP, PEC and LGA



**Current UK
Preterm Birth
Cost**

£3.53 BIL



**GrowBaby®
Preterm Birth
Savings**

75%

What's Next?

Refine

- Review of current SNPs
- Adjust Nutrigenomic test
- Addition of Patient Questionnaire
- Biomarker Recommendations & Analysis


Expand

- MCOs
- Private Insurers
- Direct to Consumer
- Government Policy
- Partners

Explore

- Principle Component Analysis
- Epigenetic Mechanisms (DNA_m, DNA_{MT}, Imprintome)





Most Risk is not hard-wired, but epigenetically modifiable!



Thank you!

- Molina[®] Healthcare
- Metagenics[®]
- DNALife[®]
- OmegaQuant[®]
- GrowBaby[®] Life Project
- GrowBaby[®] Health



References: Nutrient insufficiencies and Mat'l./Neo. Outcomes

Zinc

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DHA

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Vit D

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Longitudinal Outcomes

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