# Carenza di Folati e Supplementazione in Gravidanza

**XXIII CONGRESSO NAZIONALE A.GI.CO.**

Ferrara 17-18 Maggio 2019

**Prof. Michele Rubini**

*Dip. Scienze Biomediche e Chirurgico-Specialistiche*
*Unità di Epidemiologia Genomica e Farmacogenetica*
*Università degli Studi di Ferrara*

# Multivitamins: Help or Harm?

- …. no clear evidence of a beneficial effect of supplements on all-cause mortality, cardiovascular disease, or cancer (27 trials: 450,000 people).

  Fortmann et al., Ann Intern Med 2013

- …. multivitamins do not reduce risk for mental decline such as memory loss or slowed-down thinking (12y study: 5,947 men)

  Grodstein et al., Ann Intern Med 2013

- …. the exception is supplemental folic acid for women of child-bearing potential

  Larry Appel, M.D., Johns Hopkins Medical School

# Willis Factor


1930s, Mumbai, India:
L'estratto di lievito previene l'anemia macrocitica in donne gravide

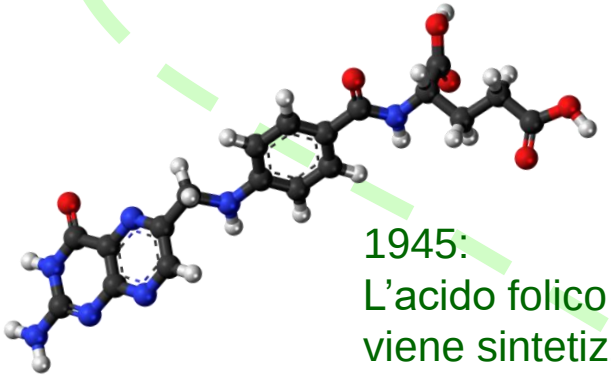
Lucy Willis

# Acido Folico


1930s, Mumbai, India:
L'estratto di lievito previene l'anemia macrocitica (Willis factor)

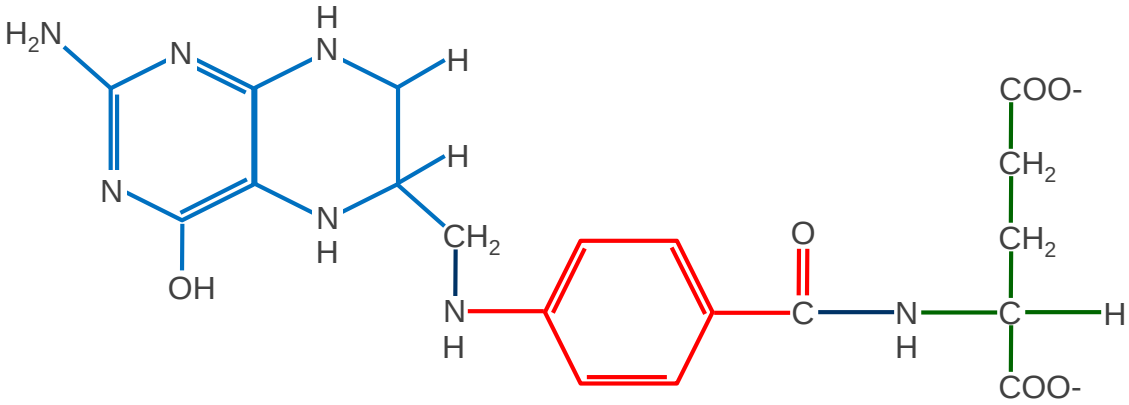
Lucy Willis

1941:
Il Willis Factor viene isolato dagli spinaci e chiamato Acido Folico



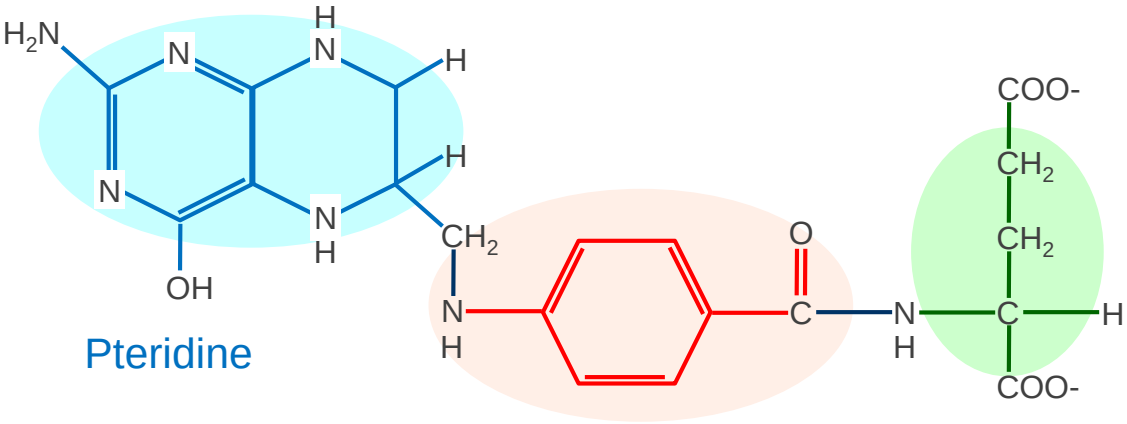
1945:
L'acido folico (PGA) viene sintetizzato

Robert Stokstad




*Michele Rubini, University of Ferrara*

# Folates



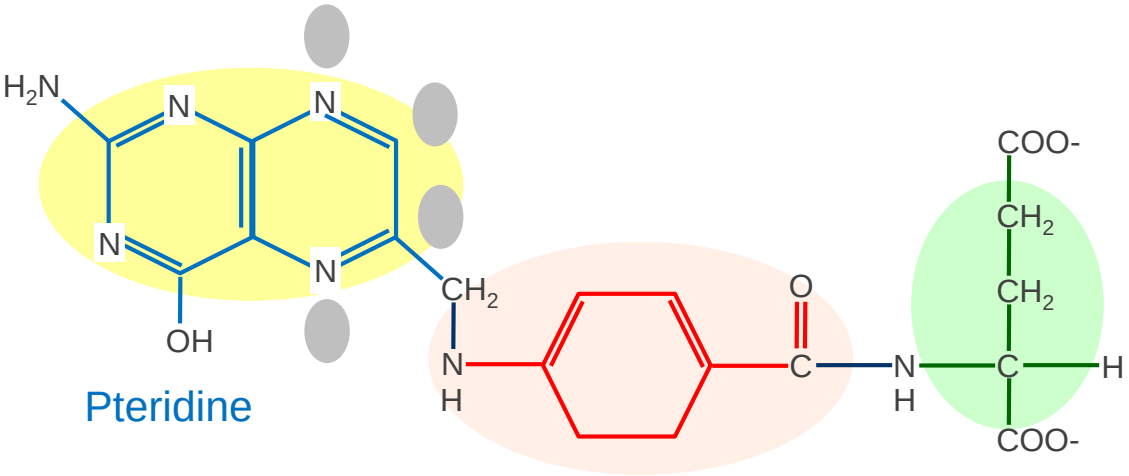

Pteridine

p-Aminobenzoate

Glutamate

# Folic acid

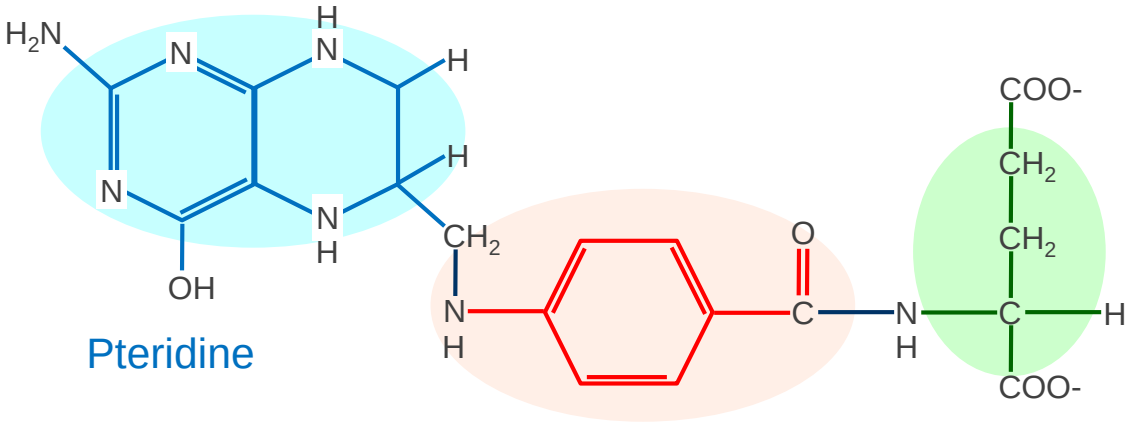
Pteroyl-Monoglutamic Acid (PGA)




Fully Oxidized

- Synthetic form of vit-B9
- Completely oxydized

# Natural Folates




Pteridine

p-Aminobenzoate

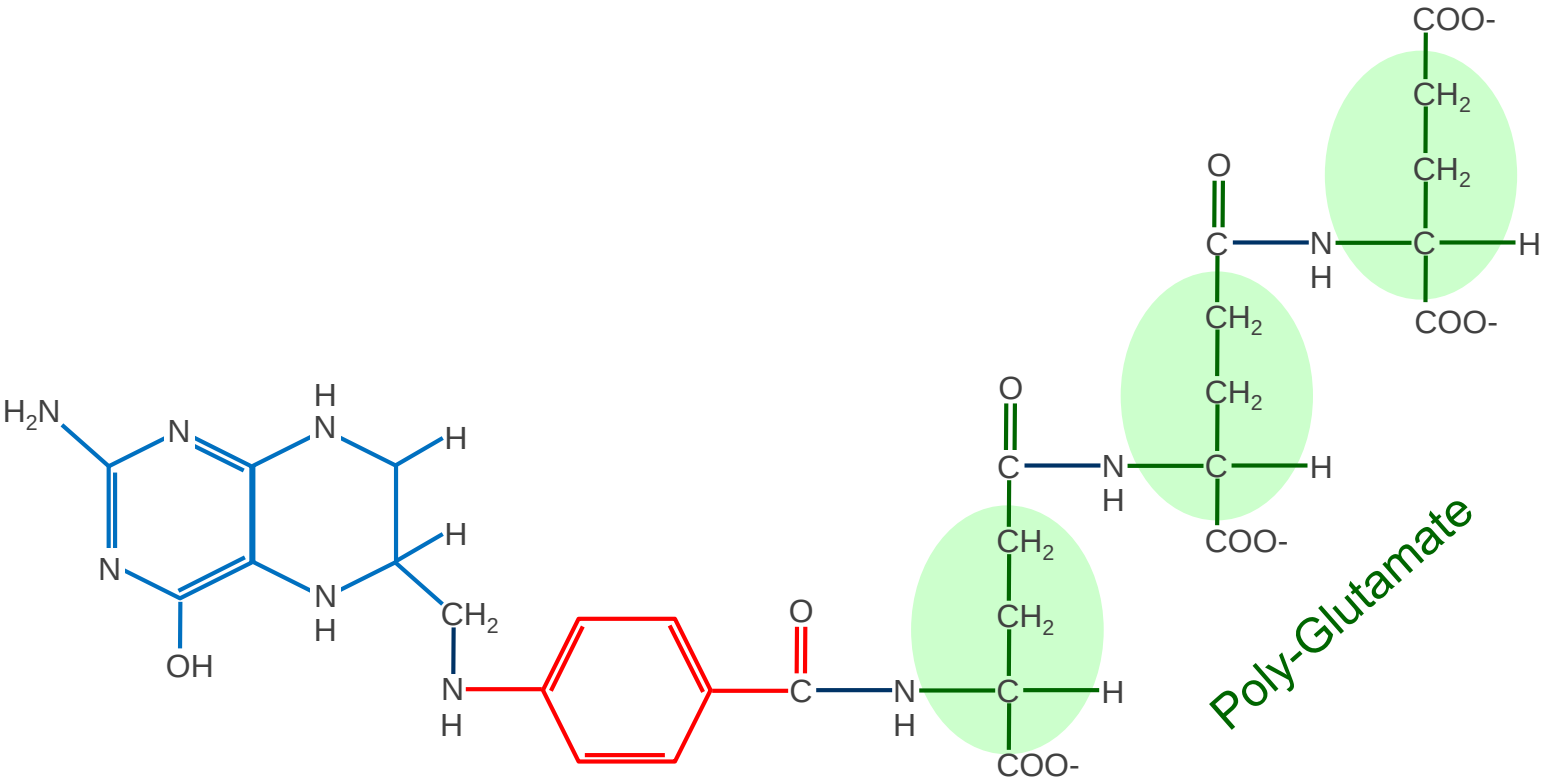
Glutamate

Reduction

1C moiety

Poly-Glu

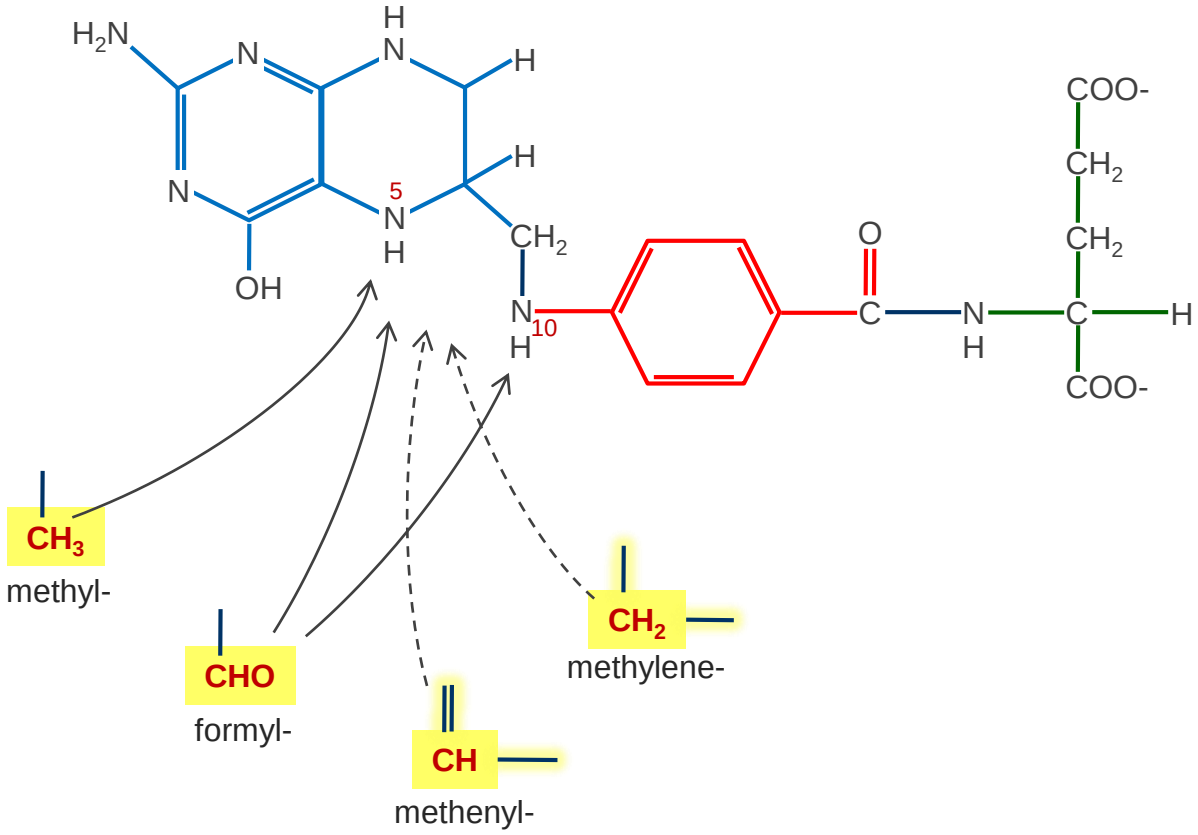
# Natural Folates




$(Glu)_{4-8}$

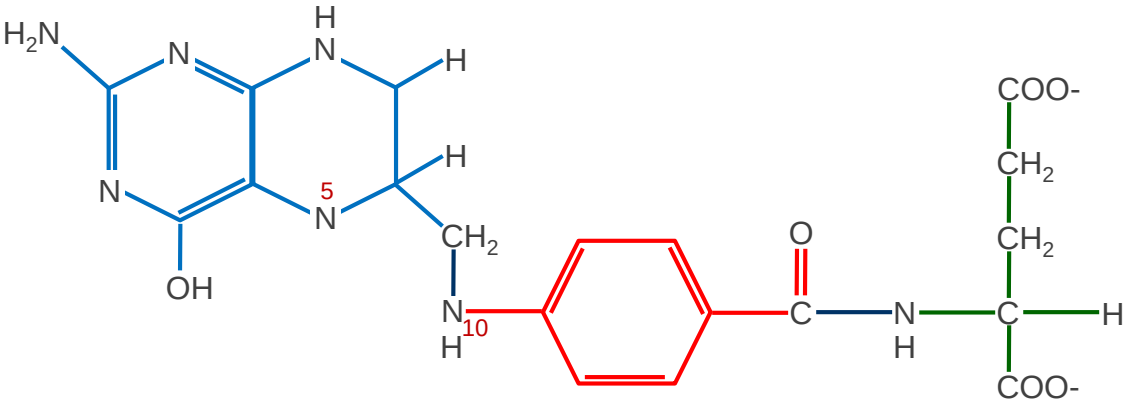
*Michele Rubini, University of Ferrara*

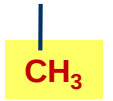
# Substitution of one 1C unit in $N_5$ e $N_{10}$



# 5-Methyl-Tetrahydrofolate

- Predominant natural folate
- Highly stable
- Ready vitamer
- Required for Hcy methylation




methyl-

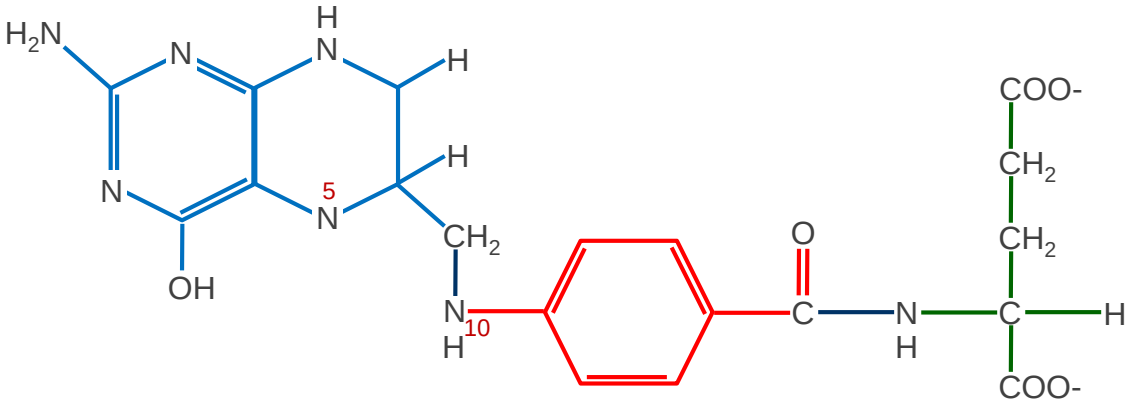

formyl-


methenyl-


methylene-

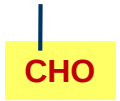
# 5-Formyl-Tetrahydrofolate

- Natural folate
- Highly stable
- Not serving as 1C donor
- *Leucovorin*



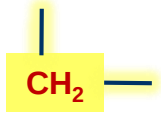


methyl-




formyl-

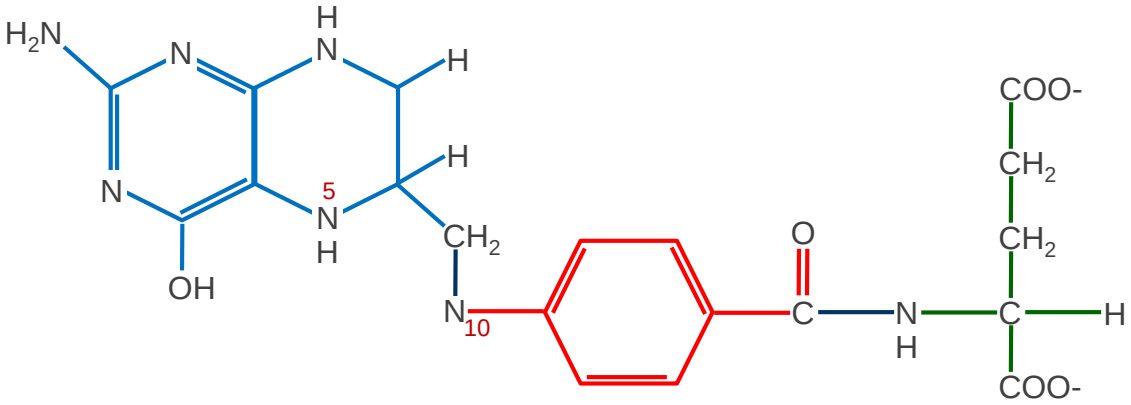

methenyl-




methylene-

# 10-Formyl-Tetrahydrofolate

- Very unstable
- Synthesis of purines





methyl-

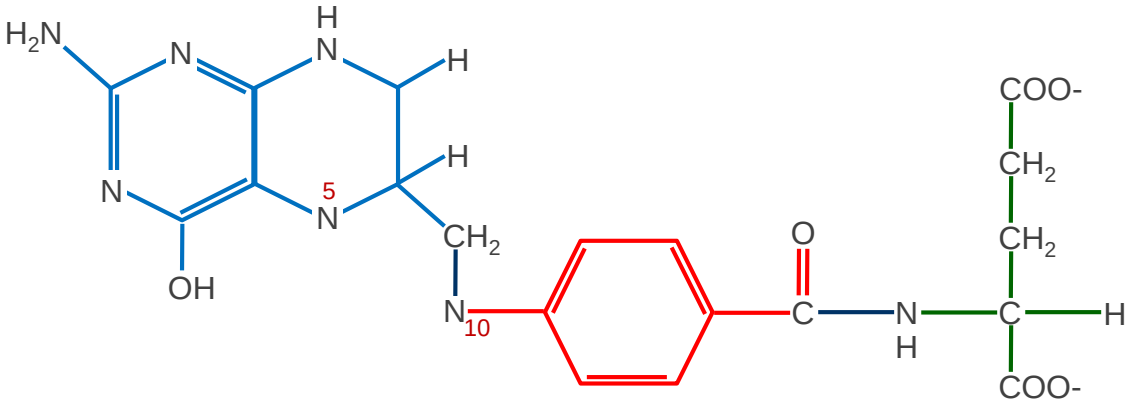

formyl-

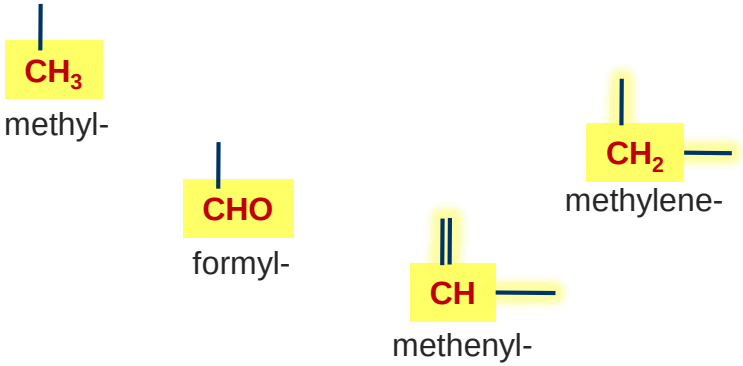

methenyl-


methylene-

# 5,10-Methenyl-Tetrahydrofolate

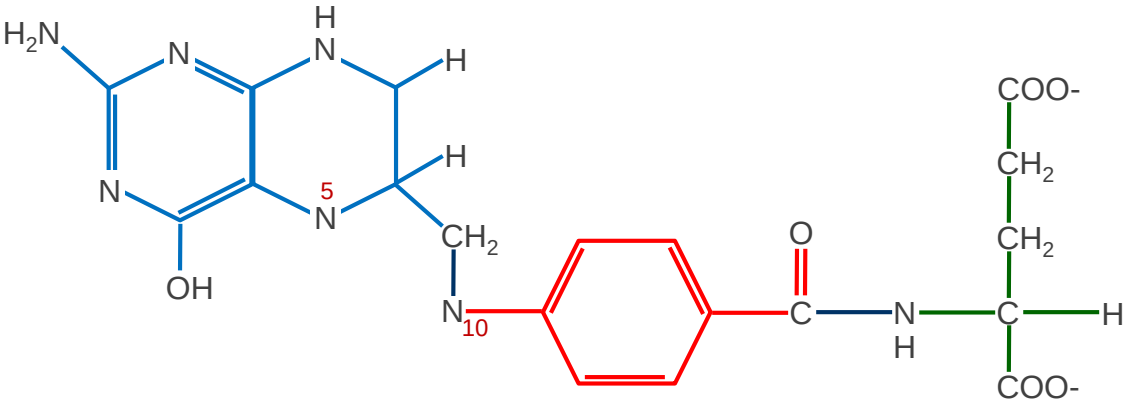
- Unstable
- Prosthetic group for DNA-pholyase

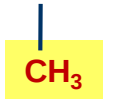


# 5,10-Methylene-Tetrahydrofolate

- Required for Thymidilate synthesis



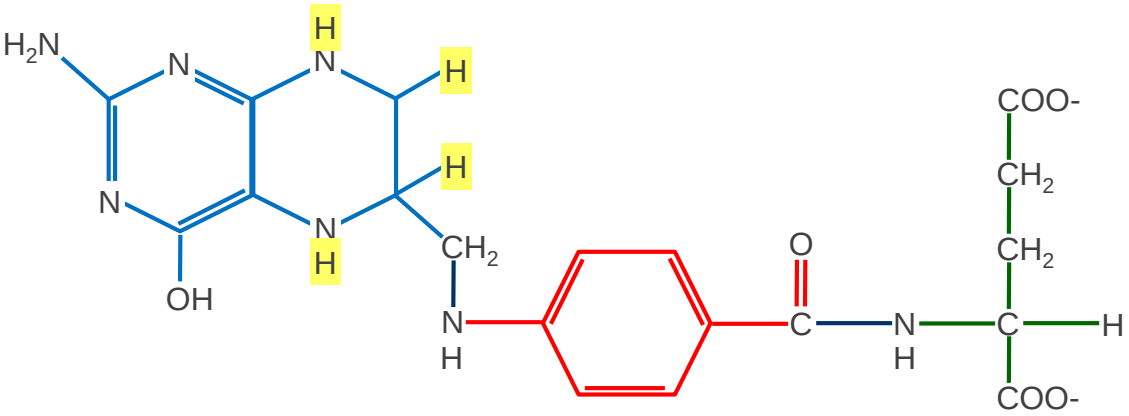

methyl-


formyl-


methenyl-


methylene-

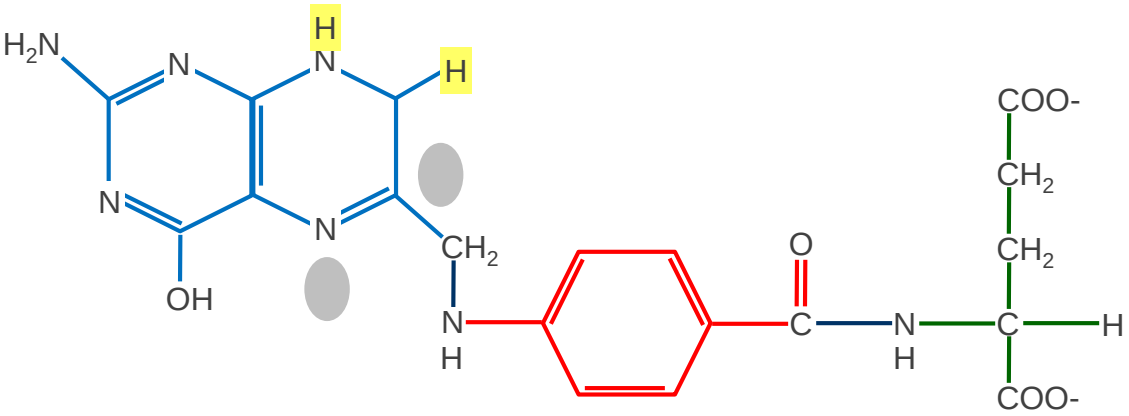
# Tetrahydrofolates




- Reduced folates
- Natural vitamers

- Nutrition: 50% bioavailability
- Supplement: 100% bioavailability

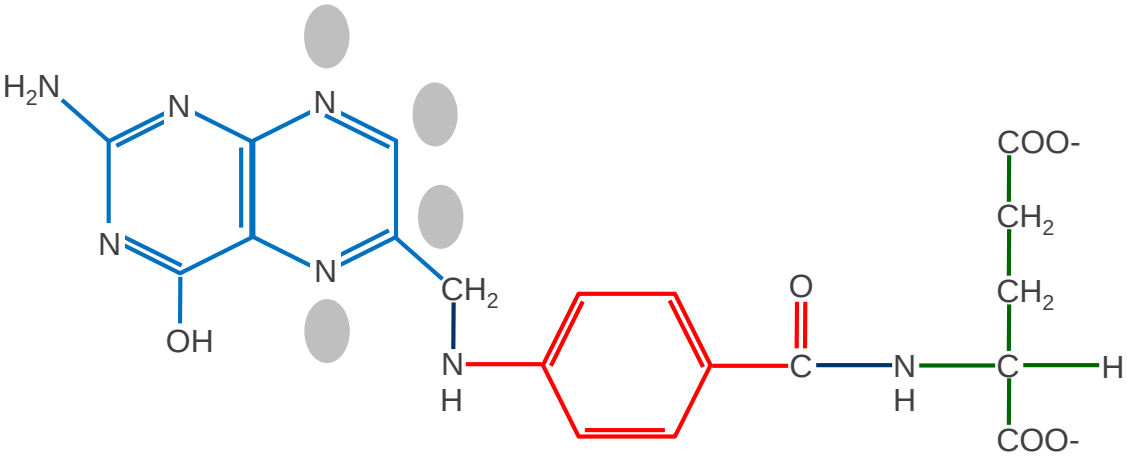
# Dihydrofolates




- Partly oxydized
- Unstable in acid condition (postprandial stomach)
- Rescued by ascorbic acid

# PGA Folic acid

pteroyl-monoglutamic acid

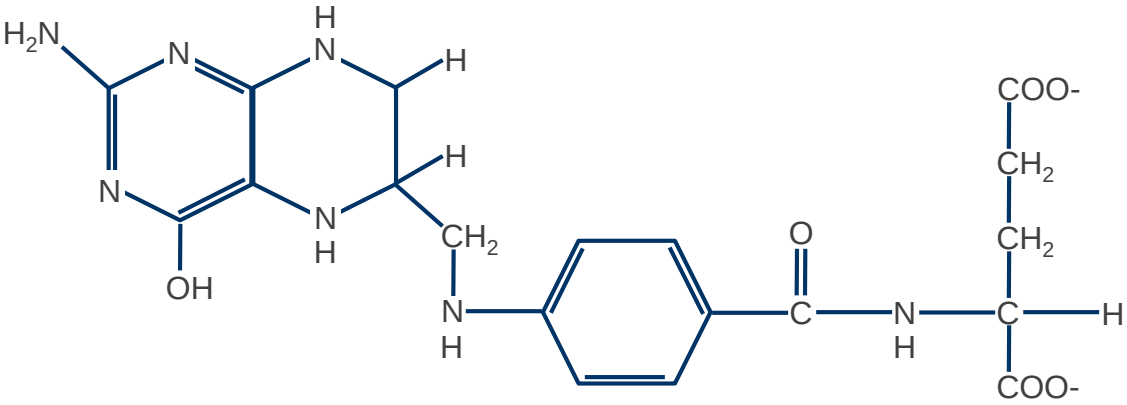



- Synthetic form of vit-B9
- Completely oxydized
- Highly stable
- Pro-vitamer: needs conversion to THF

- Supplement: 100% bioavailability
- Fortification: 85% bioavailability

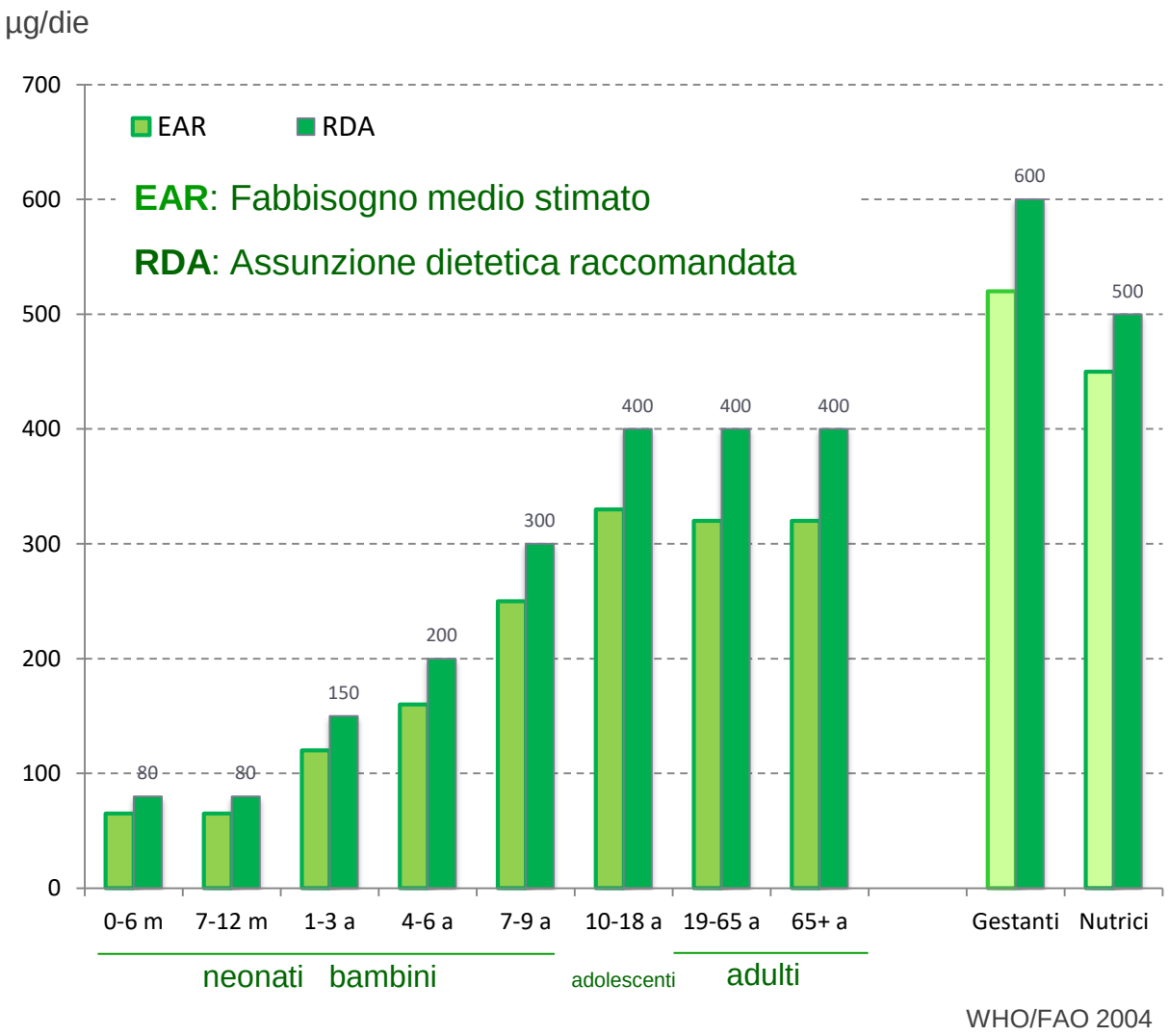
# Folati

- Vitamina B9
- Origine vegetale o microbiologica
- Idrosolubile ⇨ limitati depositi nell'organismo



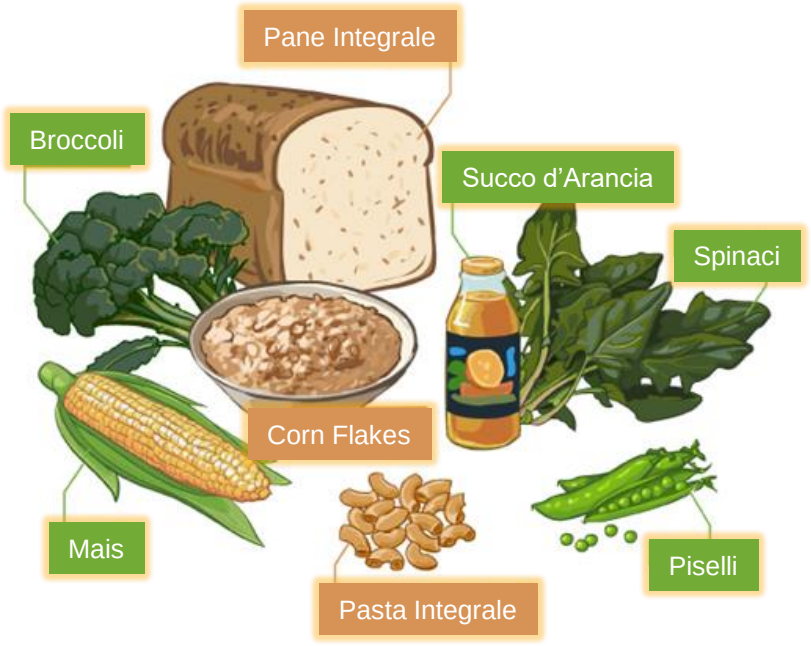

- Trasferiscono unità mono-carboniose
- Sintesi di acidi nucleici e aminoacidi
- Metilazione genomica
- Stabilità genomica
- Necessari soprattutto per tessuti con proliferazione e differenziamento cellulare

# Fabbisogno di Folati




WHO/FAO 2004

# Assunzione di Folati




- Dieta 1µg = 1µg Folato equivalente
- Alimenti fortificati con acido folico
  1µg = 1.7µg Folato equivalente

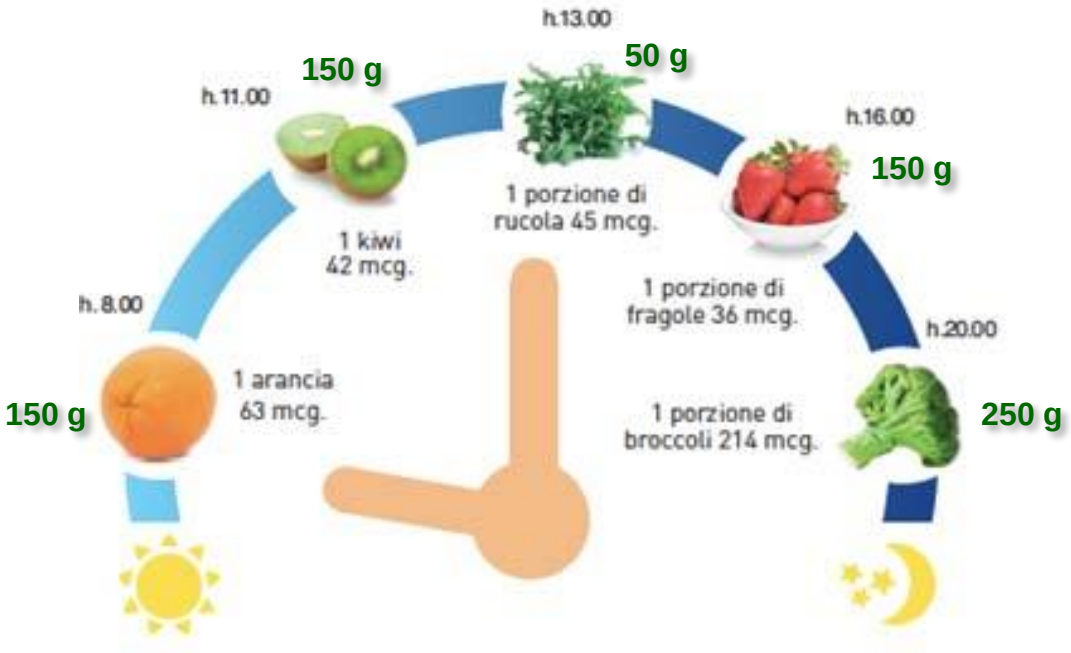
- Supplementazione
  - Acido Folico
  - Acido Folinico
  - Metilfolato

  1µg = 2µg Folato equivalente

# Dose giornaliera di 400µg di Folato equivalente

| | | |
|---|---|---|
| Germi di grano | | 114 g |
| Semi di soia | | 178 g |
| Fagioli | | 180 g |
| Fegato di vitello | | 333 g |
| Cavolini di Bruxelles | | 409 g |
| Spinaci | | 417 g |
| Fragole | | 645 g |
| Cavolfiore | | 651 g |
| Pane integrale | | 889 g |
| Pomodori | | 1,667 g |
| Patate | | 1,929 g |
| Mele | | 3,077 g |
| | | |

# Dose giornaliera di 400µg di Folato equivalente



# Dose giornaliera di 400µg di Folato equivalente

In Italia il **91.9%** delle donne in età fertile non assume almeno 400µg di folato al giorno

IMMIDIET project; Pounis et al., 2014, PMID: 24984999

# Folate status biomarkers

Livelli di riferimento:

| | | |
|---|---|---|
| ►Plasma Folate | 2-20 ng/ml (4-22 nM) | media: 12 ng/ml |
| ►RBC Folate | 140-960 ng/ml (550-2200 nM) | media: 250 ng/ml |
| ►Plasma HCys | 4-5-7.9 nM | |
| ►Plasma B12 | 150-400 µg/ml | |

# Carenza di Folati: Segni e sintomi

- Plasma Folate <2 ng/ml
- RBC Folate <140 ng/ml

- Cute pallida
- Inappetenza, ridotto senso del gusto
- Irritabilità, mancanza di concentrazione
- Stanchezza persistente, debolezza
- Diarrea, indigestione
- Secchezza delle fauci, gonfiore della lingua
- Anemia macrocitica

# Carenza di Folati: Cause

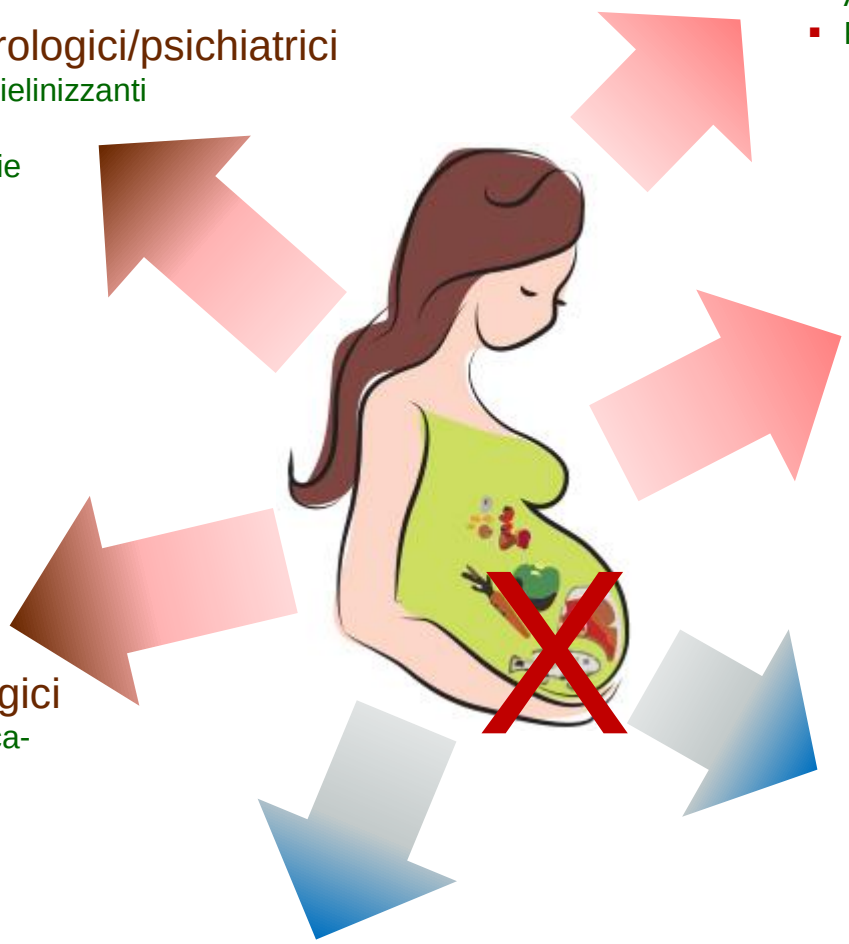
- Alterato assorbimento (p.es: celiachia)
- Alterato metabolismo (varianti genetiche)
- Assunzione di farmaci (p.es: MTX)
- Malnutrizione
- Infezioni (p.es: Giardia)
- Aumentato fabbisogno (gravidanza, allattamento)
- Esposizione a fumo
- Esposizione ad alcol
- Esposizione a luce UV

# Carenza di Folati: Conseguenze

- ►Produzione di citochine infiammatorie
- ►Alterato metabolismo dell'ossido nitrico (NO)
- ►Stress ossidativo
- ►Apoptosi cellulare
- ►Ipometilazione

# Carenza di Folati: Conseguenze

- **Alterata fertilità**
  - Alterata spermatogenesi
  - Ridotta riserva ovarica
- **Disturbi neurologici/psichiatrici**
  - Malattie demielinizzanti
  - Depressione
  - Polineuropatie
- **Iperomocisteinemia**
  - Aterogenesi
  - Disfunzioni endoteliali
    - Distacco di placenta
    - Preeclampsia
  - IUGR
  - Parto pre-termine



- **Disturbi ematologici**
  - Anemia macrocitica-megaloblastica
- **Neurocristopatie**
  - Difetti chiusura tubo neurale
  - Cardiopatie congenite
  - Schisi orofacciali
- **Aneuploidie** (non-disgiunzione meiotica)
  - S. Down


## RACCOMANDAZIONE PER LA RIDUZIONE DEL RISCHIO DI DIFETTI CONGENITI

Network Italiano Promozione Acido Folico per la Prevenzione Primaria di Difetti Congeniti

Si raccomanda che le donne che programmano una gravidanza, o che non ne escludono attivamente la possibilità, assumano regolarmente almeno 0,4 mg al giorno di acido folico per ridurre il rischio di difetti congeniti. E' fondamentale che l'assunzione inizi almeno un mese prima del concepimento e continui per tutto il primo trimestre di gravidanza.

Difetti di chiusura del tubo neurale (NTD): -50-70%

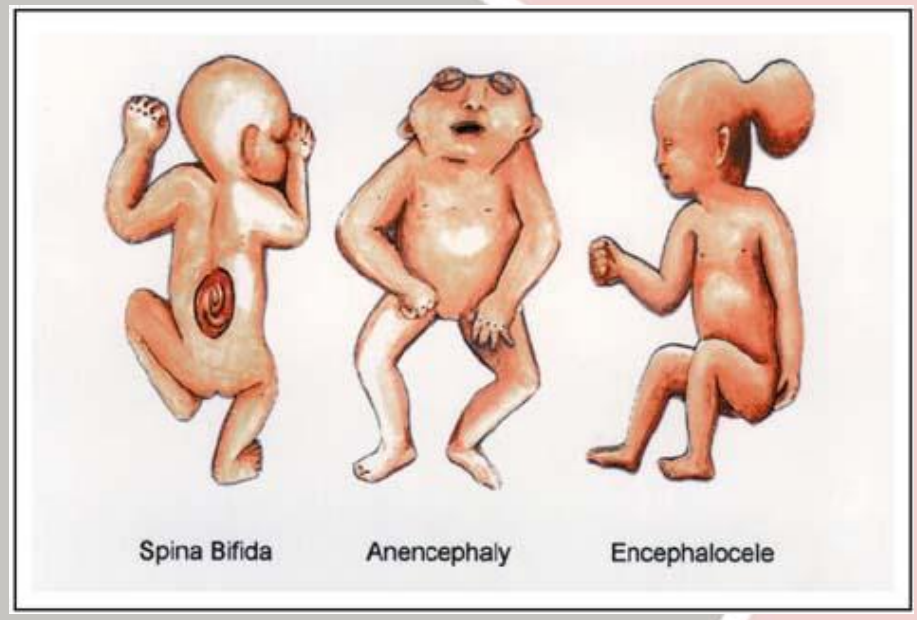
Altre anomalie congenite: -10-20%


## RACCOMANDAZIONE PER LA RIDUZIONE DEL RISCHIO DI DIFETTI CONGENITI

| | |
|---|---|
| **0.4 mg/die** | da 1 mese pre-concep.<br>fino a 3 mesi post concep**.** |
| **4.0-5.0 mg/die** | Precedente figlio NTD<br>Storia famigliare di NTD o altre malformazioni AF-prevenibili<br>Farmaci anti-epilettici<br>Obesità<br>Celiachia, Crohn disease |

Difetti di chiusura del tubo neurale (NTD): -50-70%

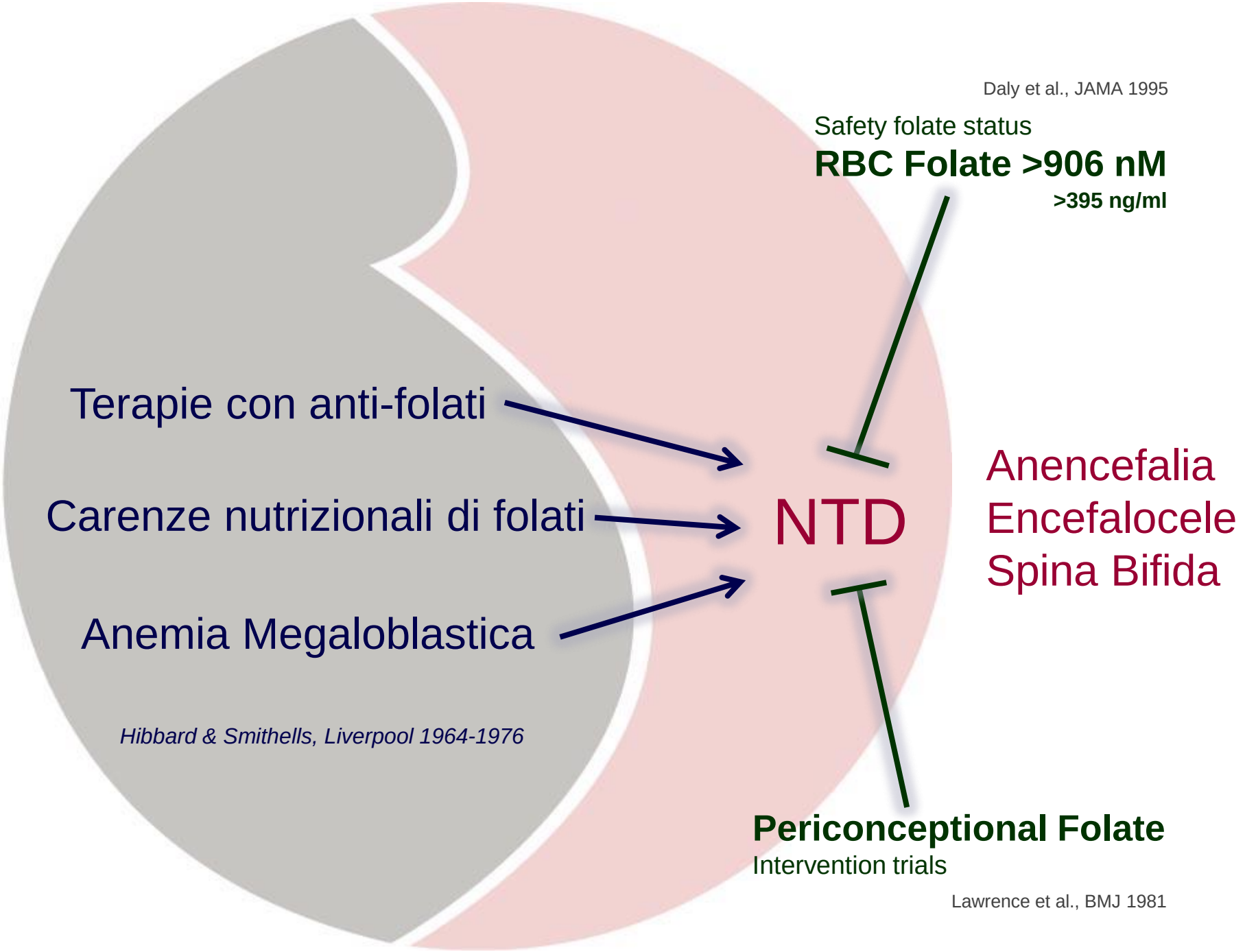
Altre anomalie congenite: -10-20%



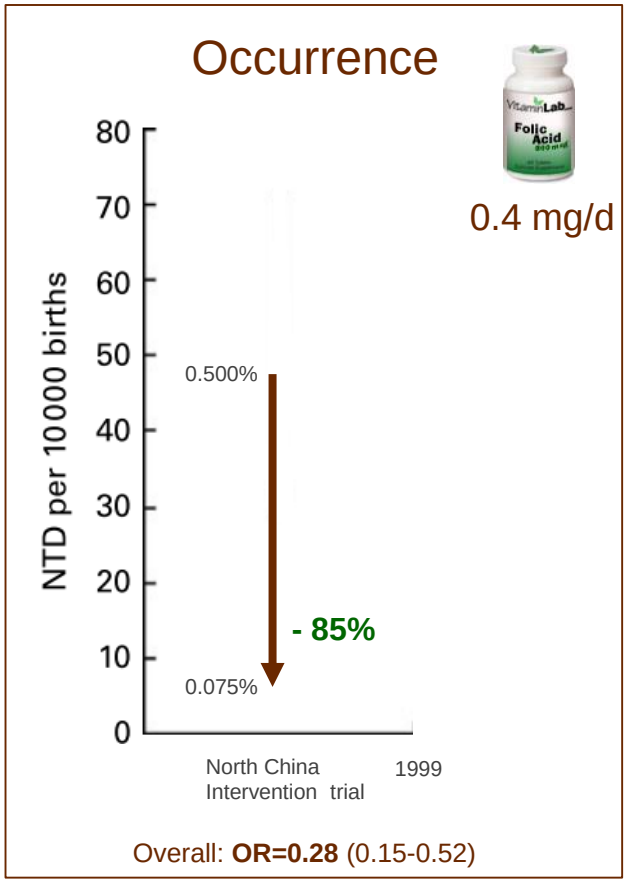

# NTD

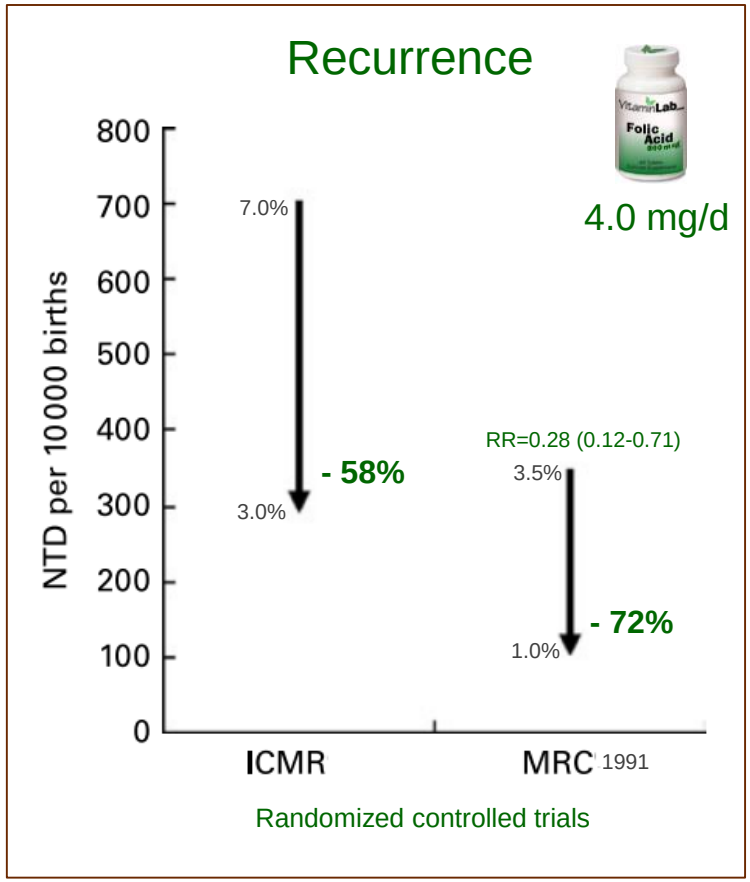
Anencefalia
Encefalocele
Spina Bifida

NTD livebirth prevalence: 1:1100 (1:660 1:2100)
(*Khoshnood et al., 2015*)


Daly et al., JAMA 1995
Safety folate status
RBC Folate >906 nM
>395 ng/ml
Terapie con anti-folati
Carenze nutrizionali di folati
Anemia Megaloblastica
Hibbard & Smithells, Liverpool 1964-1976
NTD
Anencefalia
Encefalocele
Spina Bifida
Periconceptional Folate
Intervention trials
Lawrence et al., BMJ 1981

# L'Acido Folico previene i difetti di chiusura del tubo neurale (NTD)



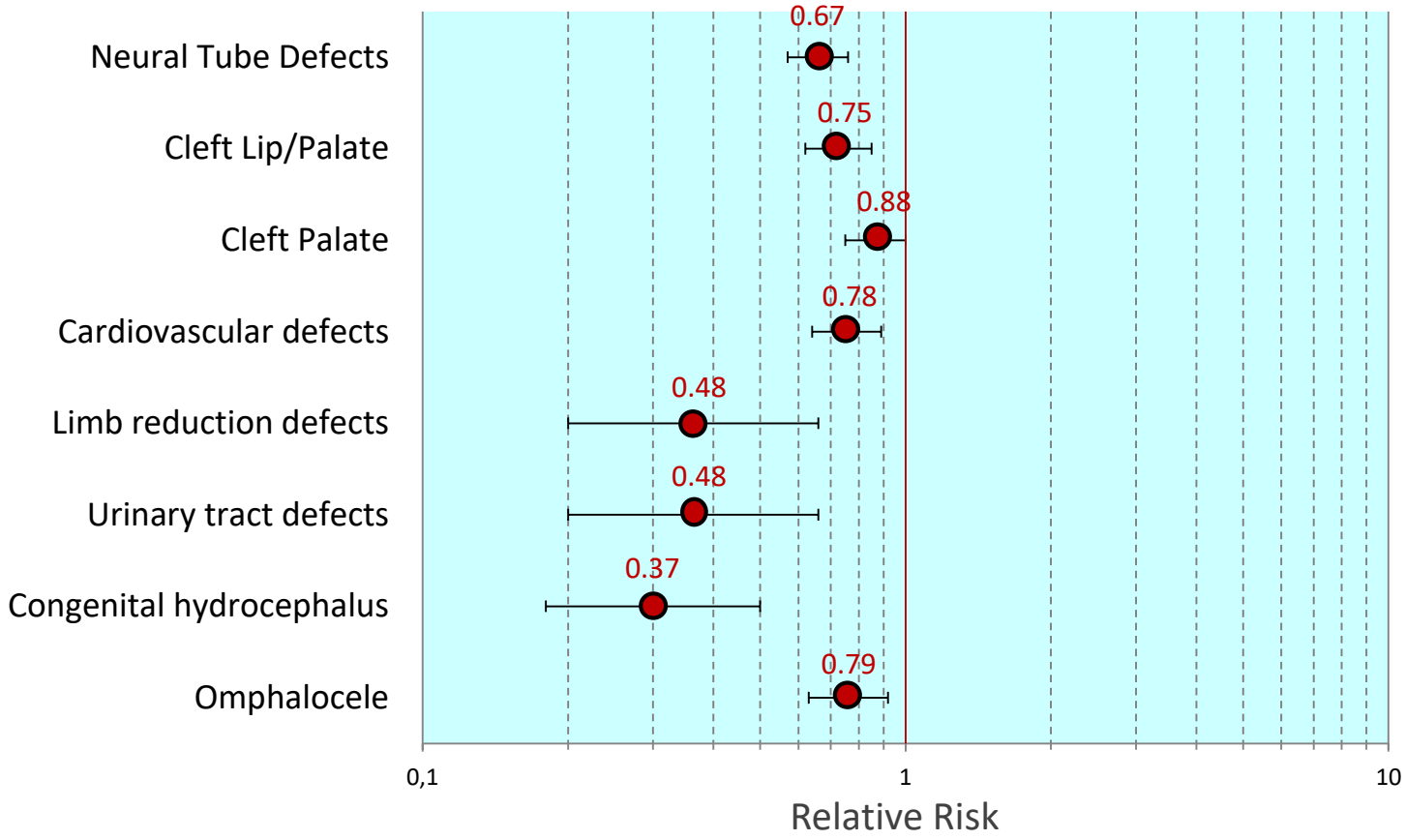

Periconceptional supplementation: -72%

Postconceptional supplementation: -45%

*Michele Rubini, University of Ferrara*

# Acido Folico: Rischio di Anomalie Congenite

## Meta-analisi di Studi Caso-Controllo

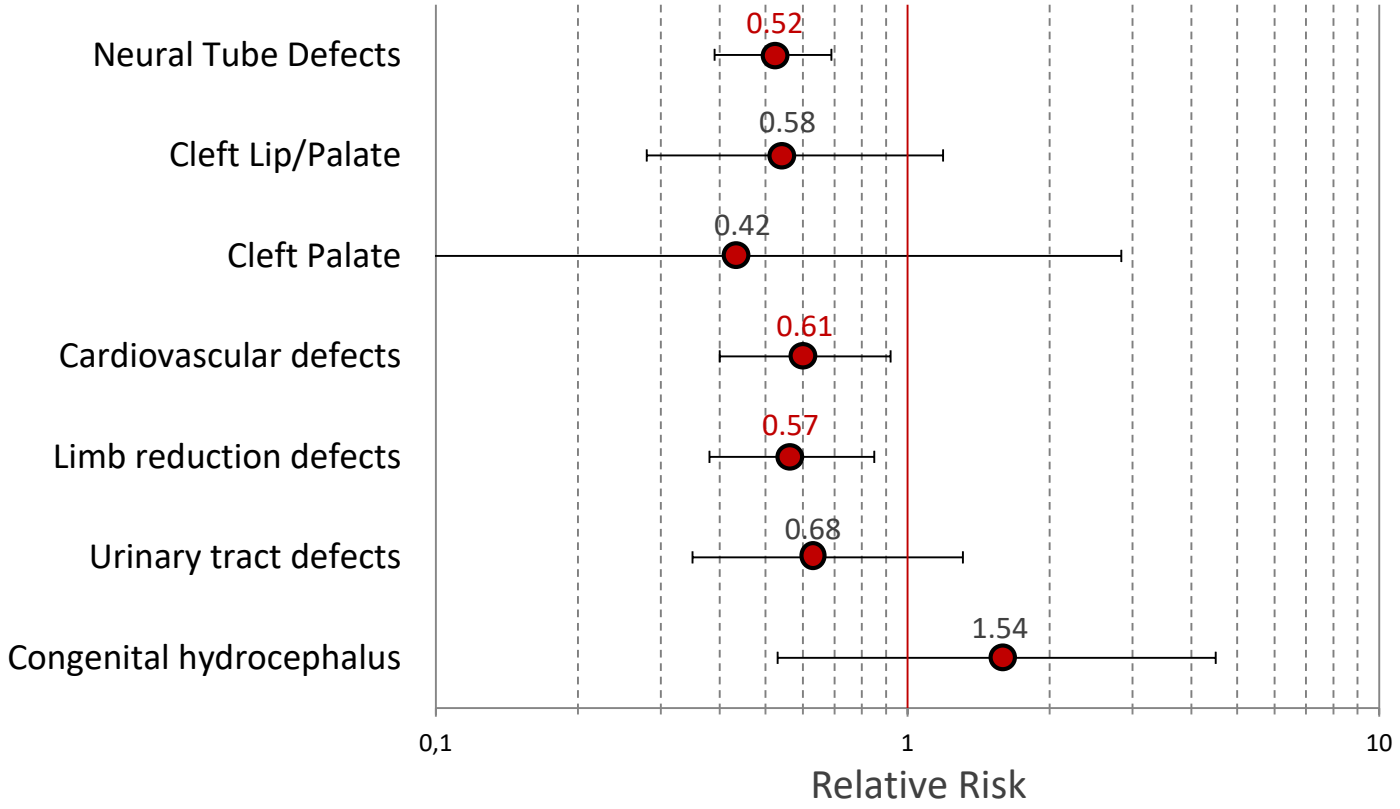




Goh et al., J Obstetr Gynecol Can 2006

Johnson and Little, Int J Epidemiol, 2008

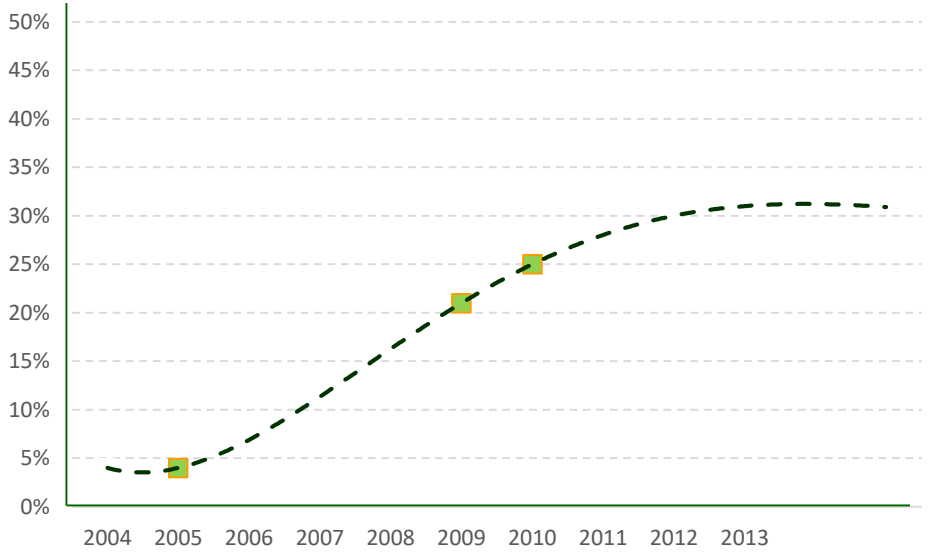
# Acido Folico: Rischio di Anomalie Congenite

Meta-analisi di Randomized Control Trials


Goh et al., J Obstetr Gynecol Can 2006

# Acido Folico: Compliance alla supplementazione periconcezionale

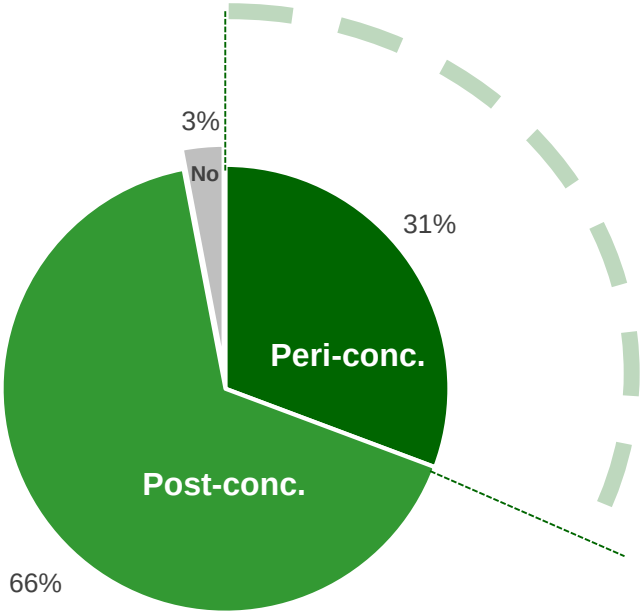



| | | |
|---|---|---|
| Età: | **≥30 anni** vs <30anni<br>70.9% | **2.37** (1.40-4.02) |
| Parità | **Primipare** vs Pluripare<br>59.2% | **2.04** (1.29-3.23) |
| Scolarità | **≥16 anni** vs <16 anni<br>34.6% | **1.77** (1.15-2.73) |
| Gravidanza | **Pianificata** vs non pianificata<br>76.9% | **3.19** (1.73-5.89) |

Casistica Italiana

Lauria et al., Rapporti ISTISAN 12/39

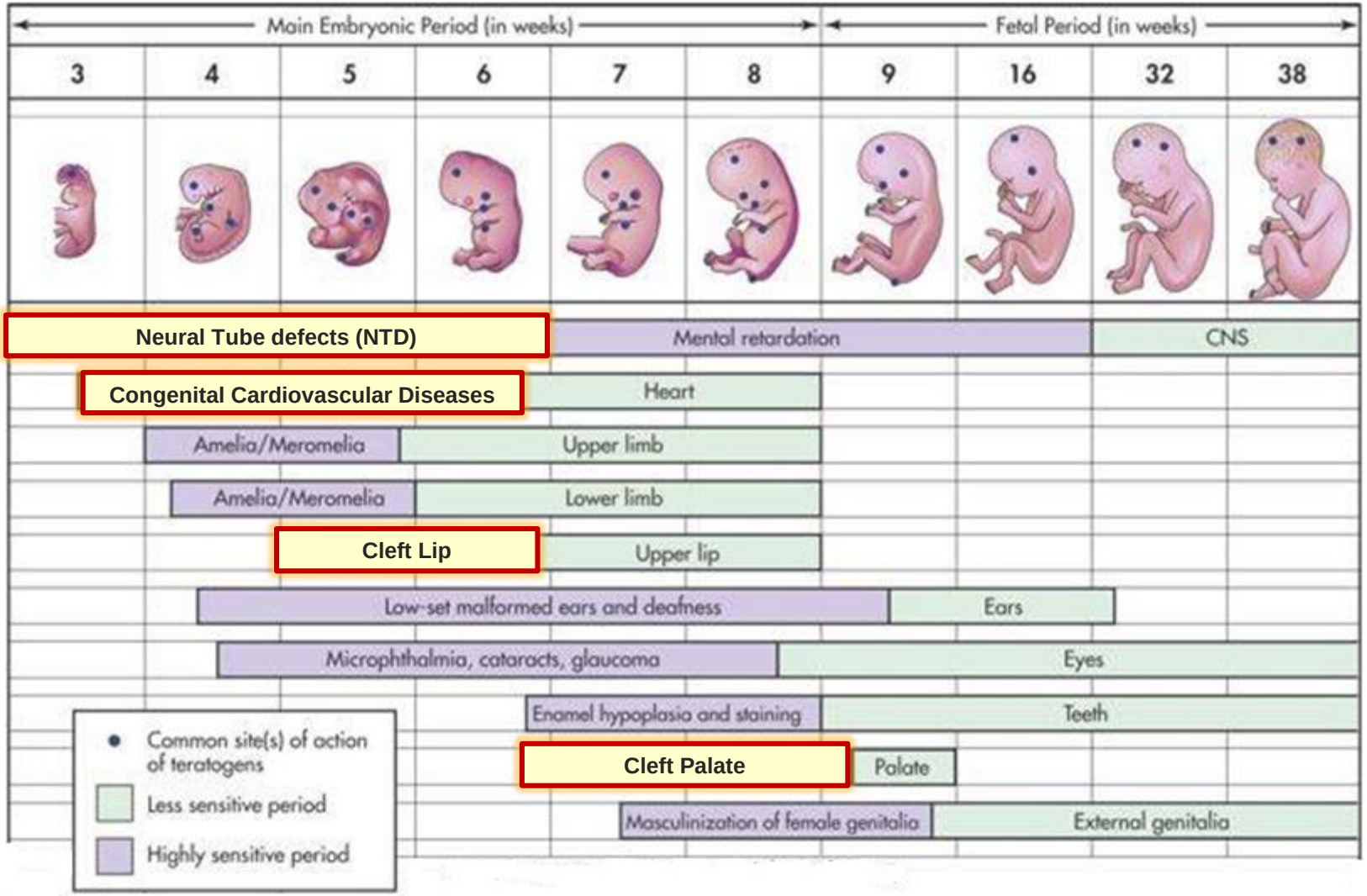
# Acido Folico: Compliance alla supplementazione periconcezionale




| | | |
|---|---|---|
| Età: | **≥30 anni** vs <30anni<br>70.9% | **2.37** (1.40-4.02) |
| Parità | **Primipare** vs Pluripare<br>59.2% | **2.04** (1.29-3.23) |
| Scolarità | **≥16 anni** vs <16 anni<br>34.6% | **1.77** (1.15-2.73) |
| Gravidanza | **Pianificata** vs non pianificata<br>76.9% | **3.19** (1.73-5.89) |

Casistica Italiana

Lauria et al., Rapporti ISTISAN 12/39




**Peri-conceptional**

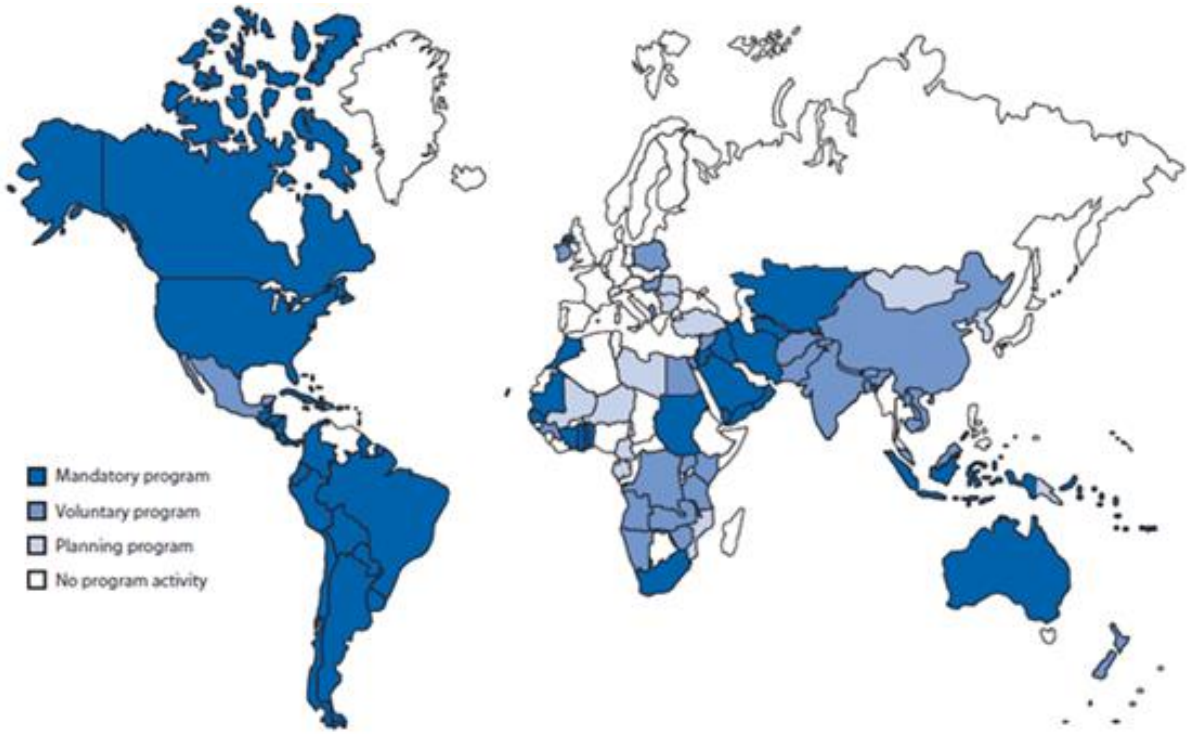
**Post-conceptional**

# Fortificazione delle farine con Acido Folico


| | |
|---|---|
| Plasma Folates (4-21 ng/ml) | + 156% |
| RBC Folates (225-640 ng/ml) | + 59% |

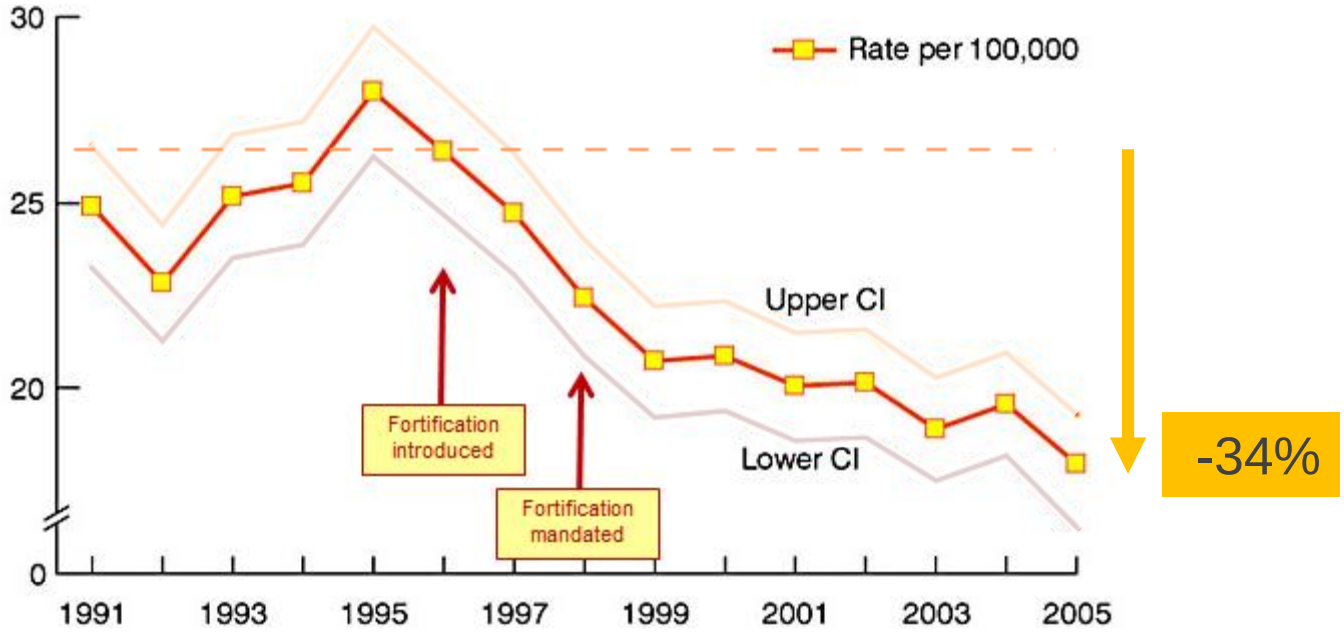
# Fortificazione delle farine con Acido Folico

*Attiva in 78 Paesi*

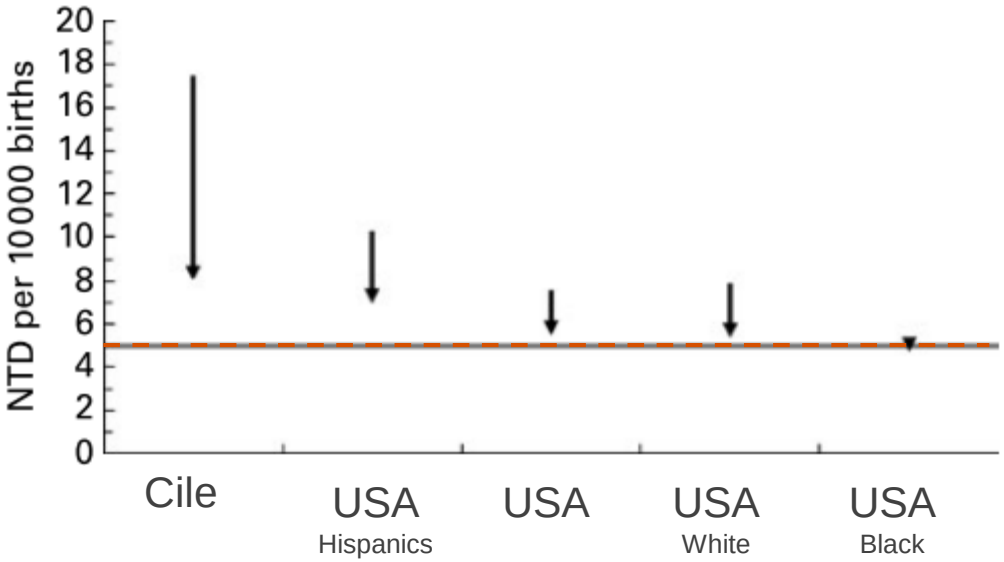



| | |
|---|---|
| Anencephaly | -20% |
| Spina bifida | -34% |
| Cleft lip/palate | -7% |
| Cleft palate | -8% |

# Incidenza di Spina bifida in USA

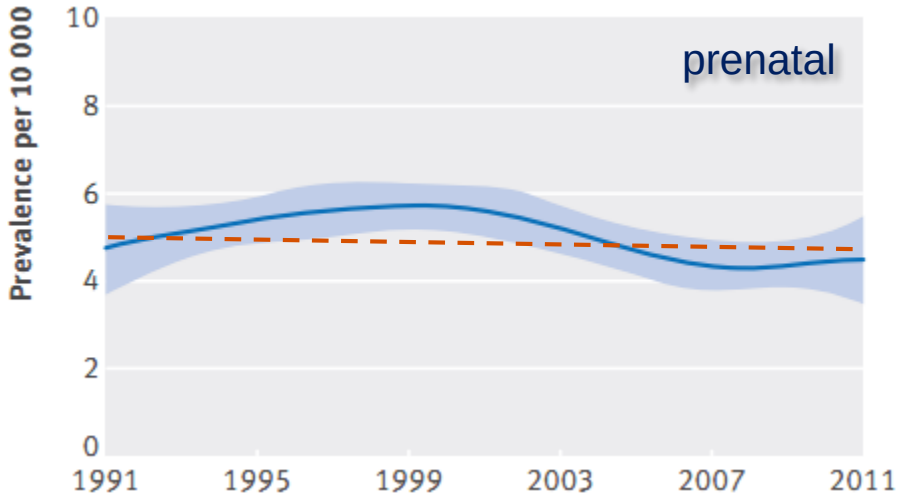


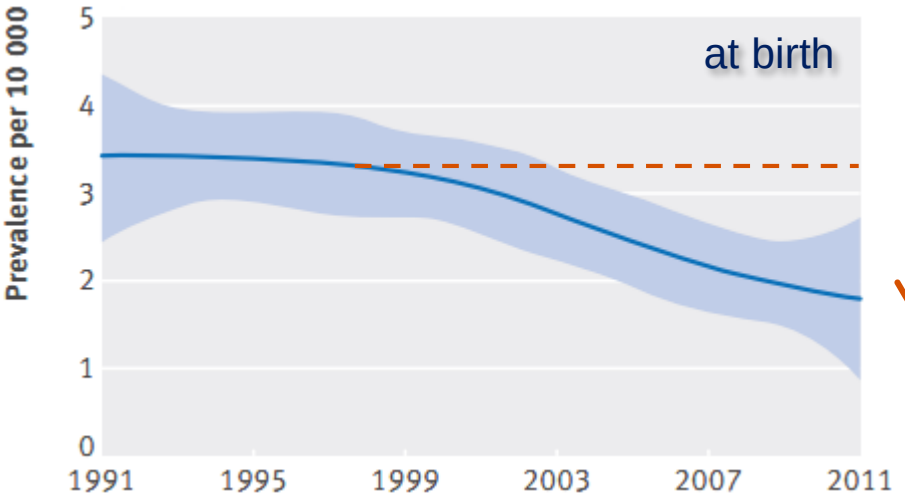
# Declino dell'incidenza di NTD dopo Fortificazione




*Heseker et al., BJN 2009*

# Incidenza di Spina Bifida in Europa




IVG

*Koshnood et al., BMJ 2015*

# Pleiotropia dell'Acido Folico

Infertilità

Gemellarità

Abortività

Preeclampsia

Prematurità

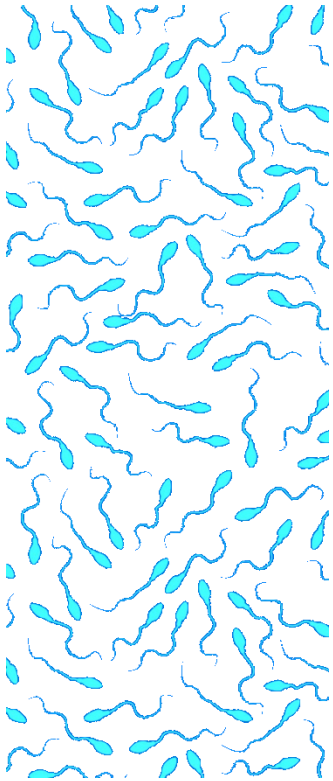
Ritardo di crescita

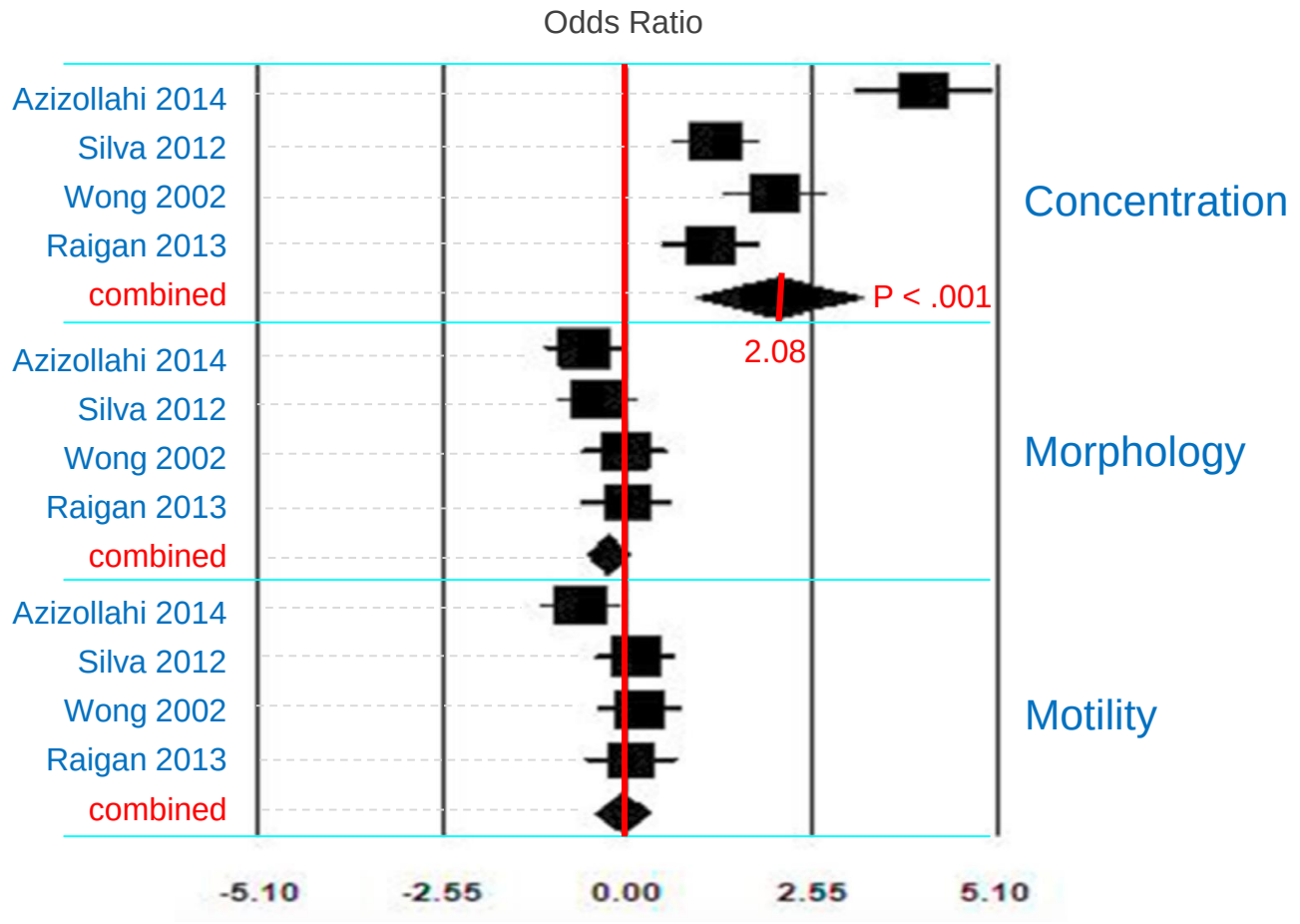
Anomalie Congenite

Neoplasie?

Autismo?

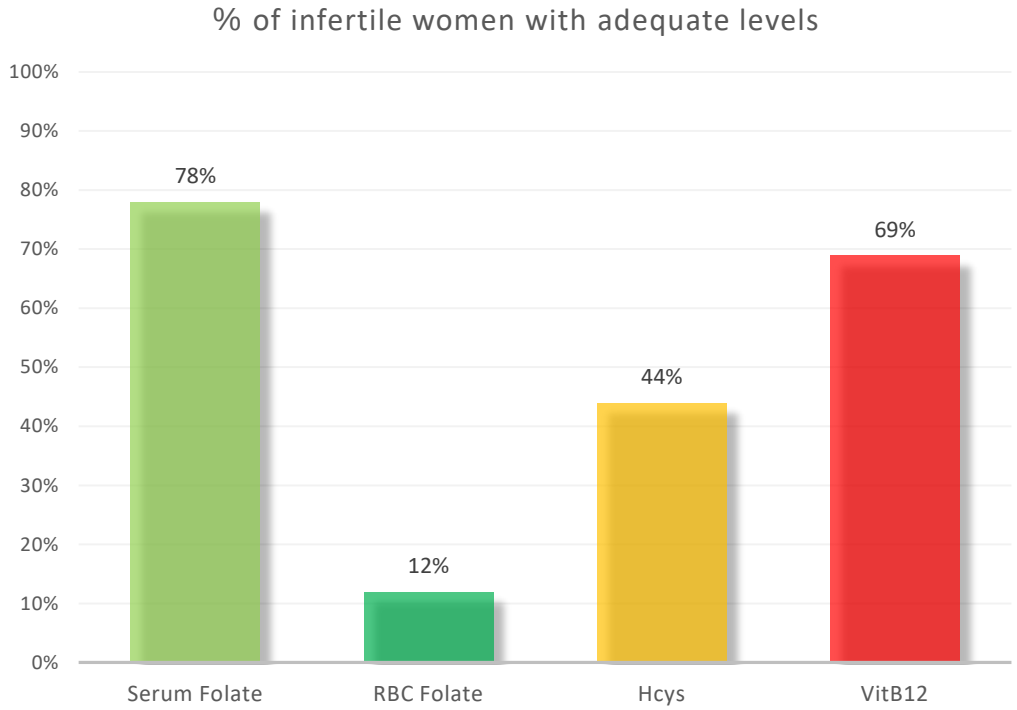

# Acido Folico e Infertilità Maschile






*Irani et al, J Urol 2017*

# Folate-related status in infertile women




*La Vecchia et al., Eur J Contracept Reprod Health Care 2017, PMID: 27976929*

# Acido Folico Preconcezionale e Infertilità Femminile

## Ovulatory dysfunction

- Higher Folate conc. and lower HCys conc. in follicular fluid
  *Boxmeer et al., 2008*
- Better embryo quality and chance of pregnancy
  *Boxmeer et al., 2009*
- Reduced risk of ovulatory infertility
  *Chavarro et al., 2008*

## Unexplained infertility

- No effect of FA supplementation

*Murto et al., Reprod Biomed Online. 2014*
*Murto et al., Acta Obstet Gynecol Scand. 2015*

# Acido Folico e Gemellarità


| | |
|---|---|
| Supplementazione preconcezionale | + **26**.0% Dizigotici |
| Fortificazione | + **4**.6% |

DZ OR=1.26 (95% CI, 0.91–1.73)
DZ+MZ OR=1.02 (95% CI, 0.84-1.24)

*Muggli & Halliday Med J Aust 2007*

# Acido Folico e Abortività / Nati Morti

*Cochrane Database Syst Rev. 2016*

40 trials (involving 276,820 women and 278,413 pregnancies)

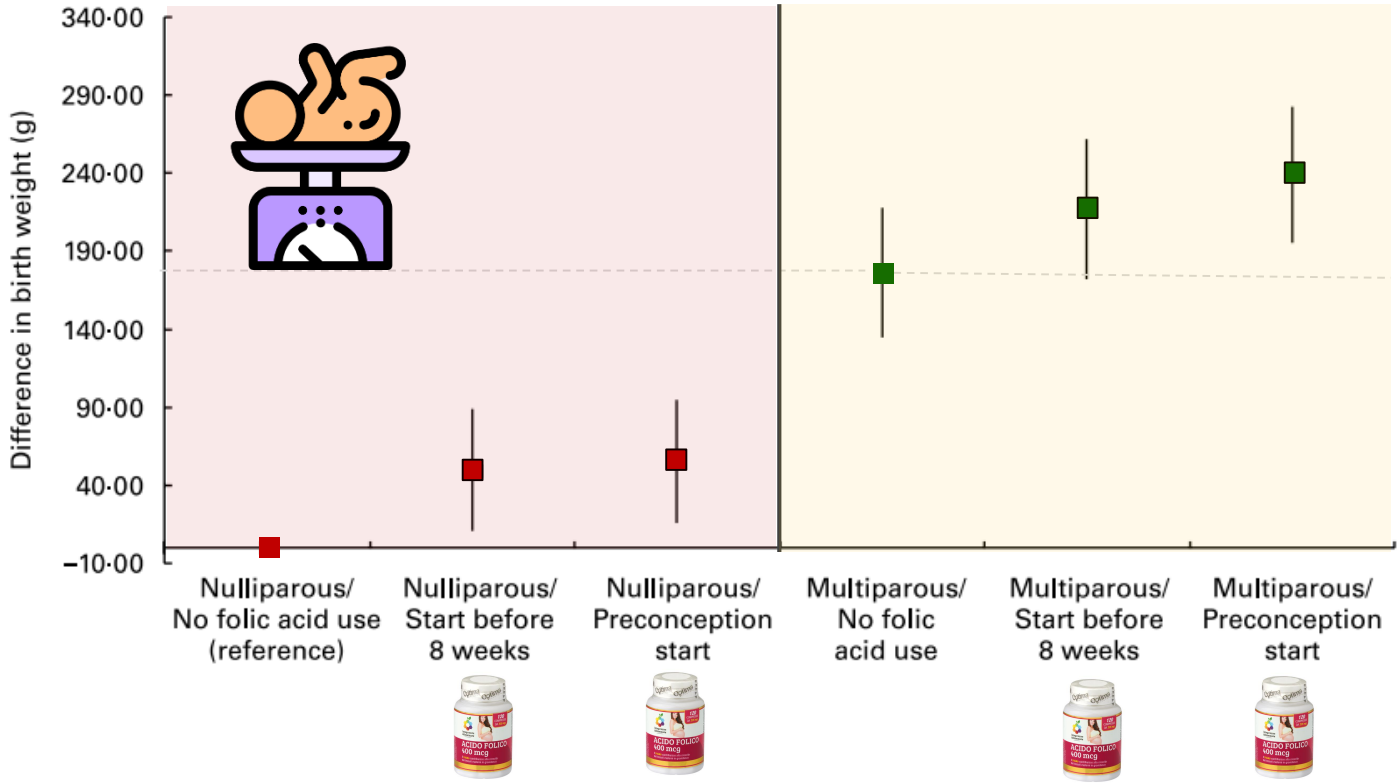
- Taking any single vitamin supplements (including Folic Acid) prior to pregnancy or in early pregnancy does not prevent women experiencing miscarriage or stillbirth
- Women receiving multivitamins plus Iron and Folic Acid had reduced risk for stillbirth

  (RR 0.92, 95% CI 0.85 to 0.99, 10 trials, 79,851 women)

# Acido Folico e Preeclampsia

- Supplementation with Multivitamin including Folic Acid in the 2nd trimester reduces the risk of preeclampsia *Wen et al., Am J Obstet Gynecol. 2008*
- HCys is an independent risk factor for gestational hypertension or PE. Folic Acid could correct hyperhomocysteinemia *Bodnar et al., Am J Epidemiol. 2006*
- No difference in effect of FA doses
  (900 women trial: **1** mg/day vs **5** mg/day) *Shahraki et al., Adv Biomed Res 2016*

# Acido Folico e Peso alla Nascita




- Preconceptional Folic Acid supplementation associates with
  - **68 g** higher birth weight (95 % CI 37.2-99.0)
  - **13 g** higher placental weight (95 % CI 1.1-25.5)
  - **- 60%** risk of SGA OR=0.40 (95% CI 0.22-0.72)

**Generation R** study: 6353 pregnancies

*Timmermans et al.,Br J Nutr 2009*

# Acido Folico e Prematurità

- Preconceptional Folic Acid ⟶ **- 12%** risk OR=0.88 (95% CI 0.63-1.21)

- Postconceptional Folic Acid ⟶ **- 25%** risk OR=0.75 (95% CI 0.55-1.02)
  Start at 8 weeks

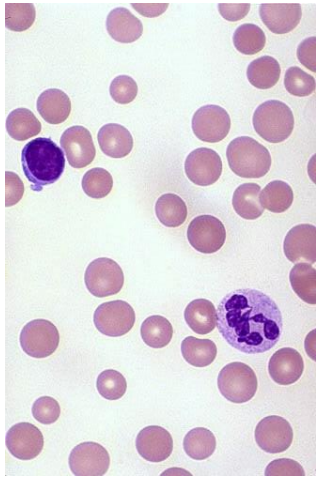
**Generation R** study: 6353 pregnancies

*Timmermans et al.,Br J Nutr 2009*

# Acido Folico e Anemia

Megaloblastic Anemia secondary to folate deficiency is a common complication in pregnancy

| Megaloblastic Anemia | | |
|---|---|---|
| | **Folate-deficiency** | **VitB12-deficiency** |
| MCV | >100 | >100 |
| Smear | Macrocytosis with hypersegmented neutrophils | Macrocytosis with hypersegmented neutrophils |
| Pernicious anemia | No | Yes |
| Hcys | Elevated | Elevated |
| Methylmalonic acid | Normal | Elevated |



Serum Folate < 2.0 ng/ml
RBC Folate < 160 ng/ml

Serum Folate: high
RBC Folate: low

Neurological lesions

**Prevents**
Folate-dependent Megaloblastic Anemia

**Masks**
the symptoms of B12-deficiency

Level of B12 should be measured before starting folic acid supplementation


Folic Acid supplement

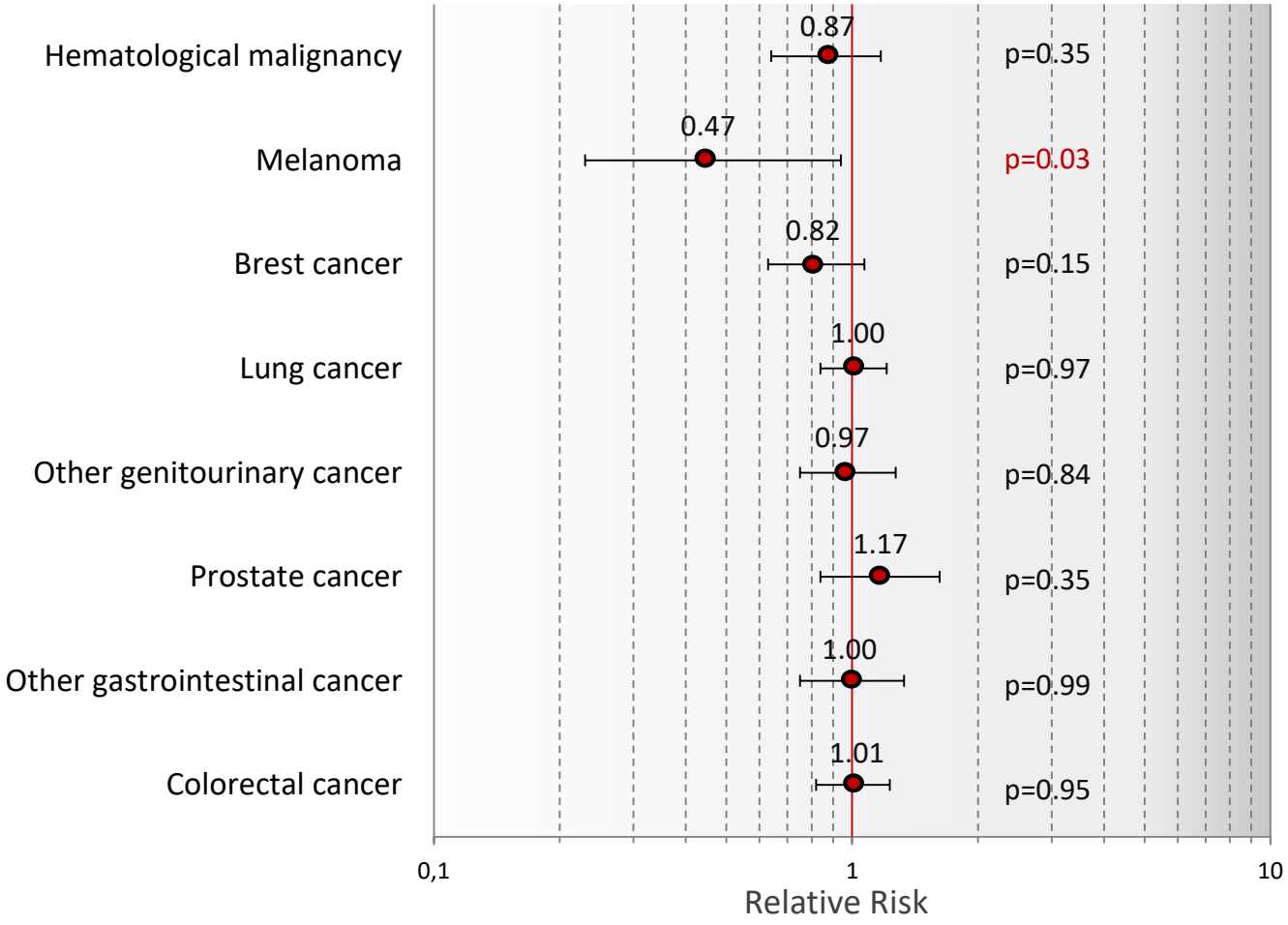
*Michele Rubini, University of Ferrara*

# Acido Folico e Rischio di Tumore

Meta-analisi di 13 trials: N=49406, **RR = 1.05 (95% CI: 0.99–1.11)**, p=0.13

(individui ad aumentato rischio di patologia cardiovascolare)

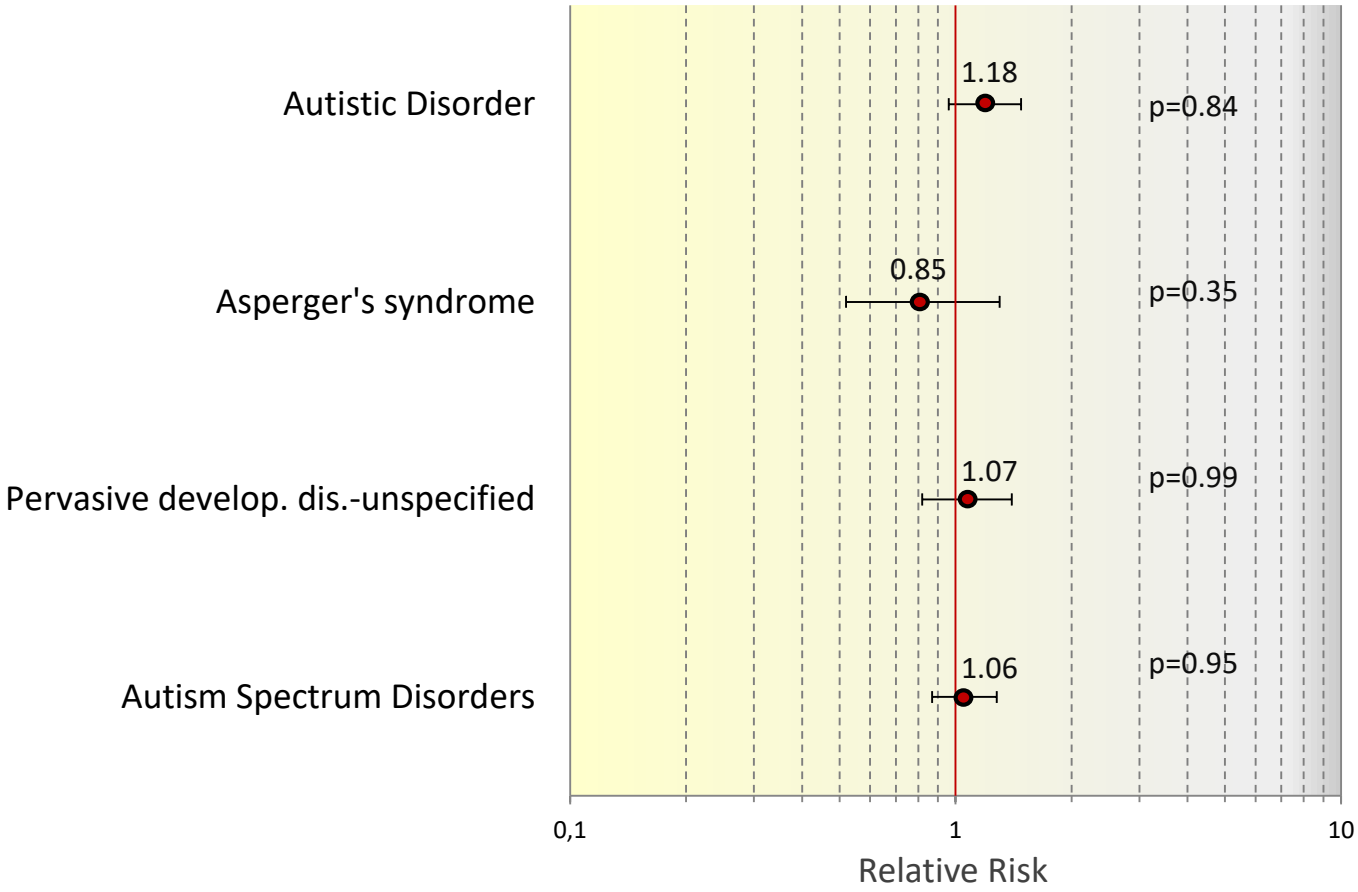
*Quin et al., Int. J. Cancer 2013*




# Acido Folico e Rischio di Patologie dello Spettro Autistico

Supplementazione periconcezionale (-4/+8 sett) con 400 ug/d

*Virk et al., Autism, 2016*




- FA: optimal protective effect if taken preconceptionally and in early pregnancy

*Moussa et al., Futur Sci 2017*

| | preconception | 1° trimester | 2° trimester | 3° trimester |
|---|---|---|---|---|
| NTD | ☺ ☺ | ☺ ☺ | 😐 | 😐 |
| Cleft Lip/Palate | ☺ | ☺ | 😐 | 😐 |
| Miscarriage | 😐 | 😐 | 😐 | 😐 |
| Preeclampsia | ☺ | ☺ | ☺ ☺ | ☺ |
| Anemia | ☺ | ☺ | ☺ | ☺ |
| FGR, SGA | ☺ ☺ | ☺ ☺ | ☺ | ☺ |
| Autism | ☺ | ☺ | 😐 | 😐 |




Folati naturali
?

Dieta

Esposoma

Efficacia

**Plasma Folate >50 nM**

*Steven et al., Sc Rep, 2018*

**RBC Folate >906 nM**

*Daly et al., JAMA 1995*

Genetica

Dose
Ottimale
?



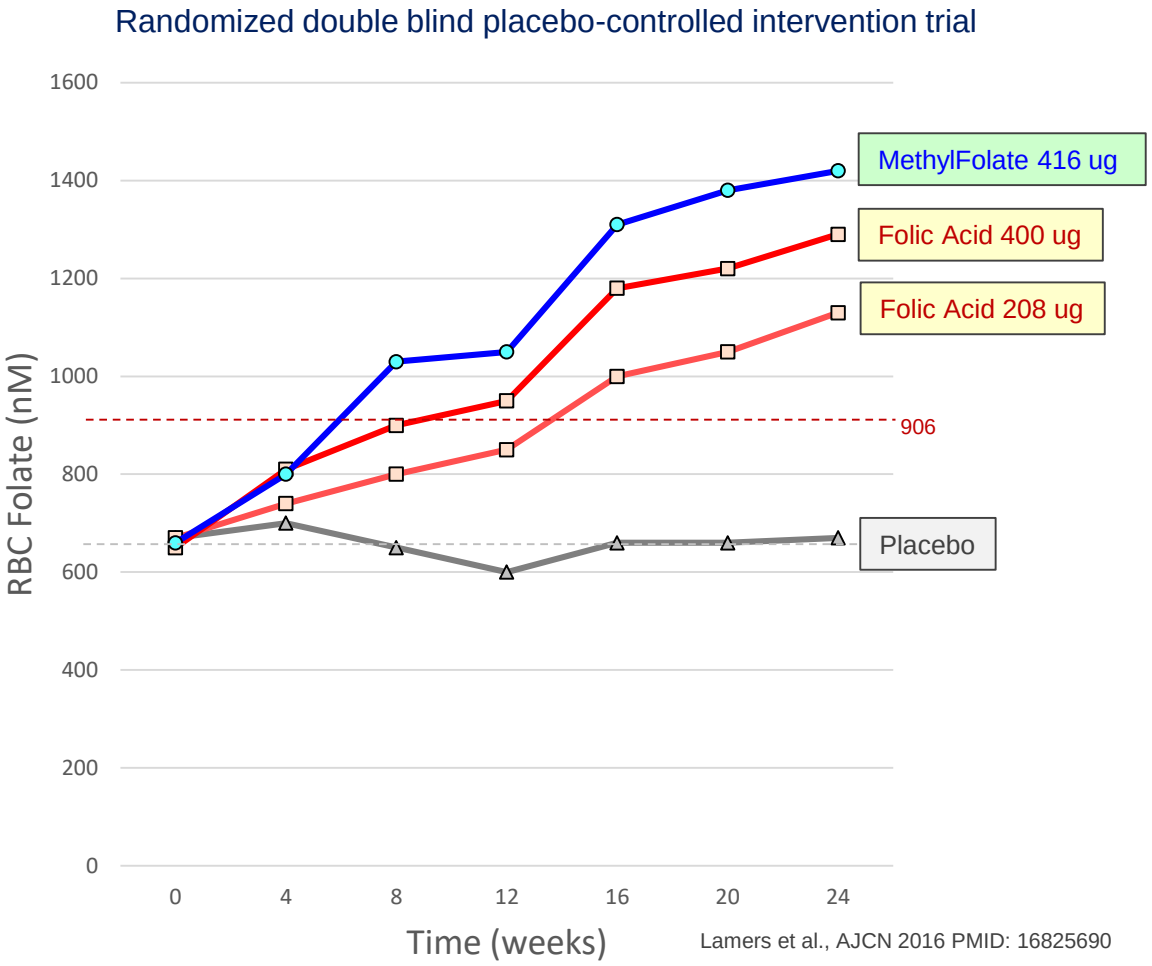
VS

MetilFolato

Acido Folico

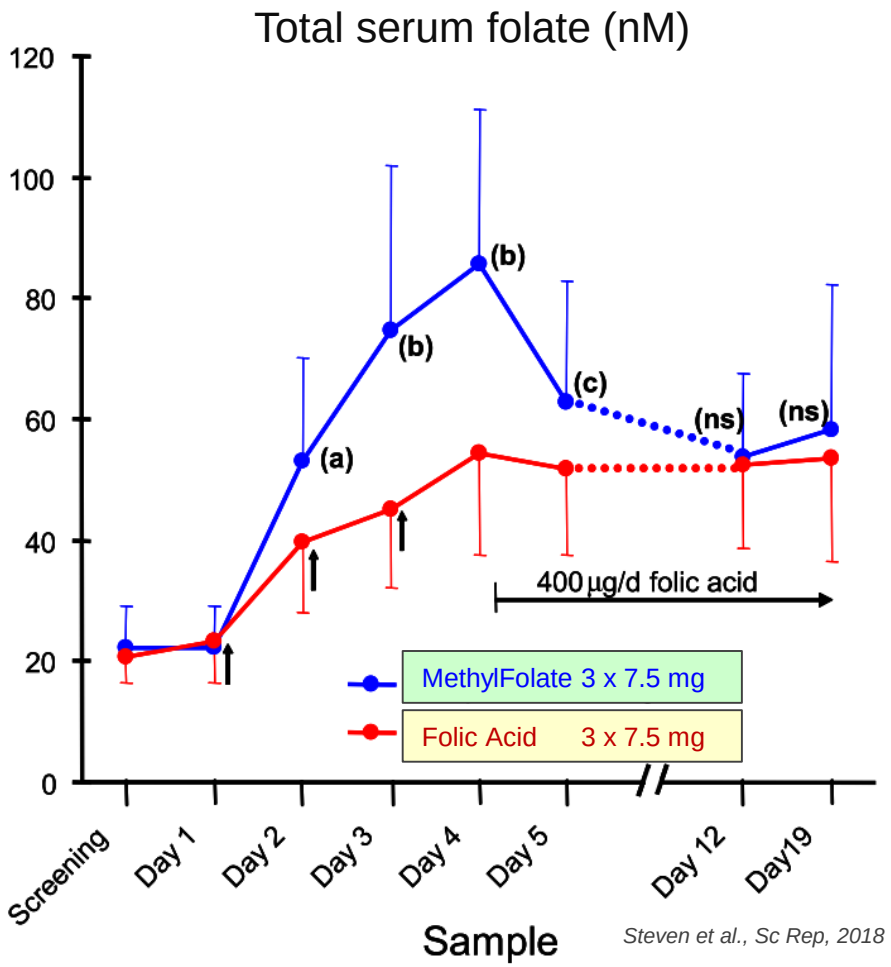

# Somministrazione di MetilFolato o Acido Folico in donne gravide

## e con carenza di folati eritrocitari




- La supplementazione con **MetilFolato** è più efficace dell'**Acido Folico** nel migliorare lo stato dei folati eritrocitari

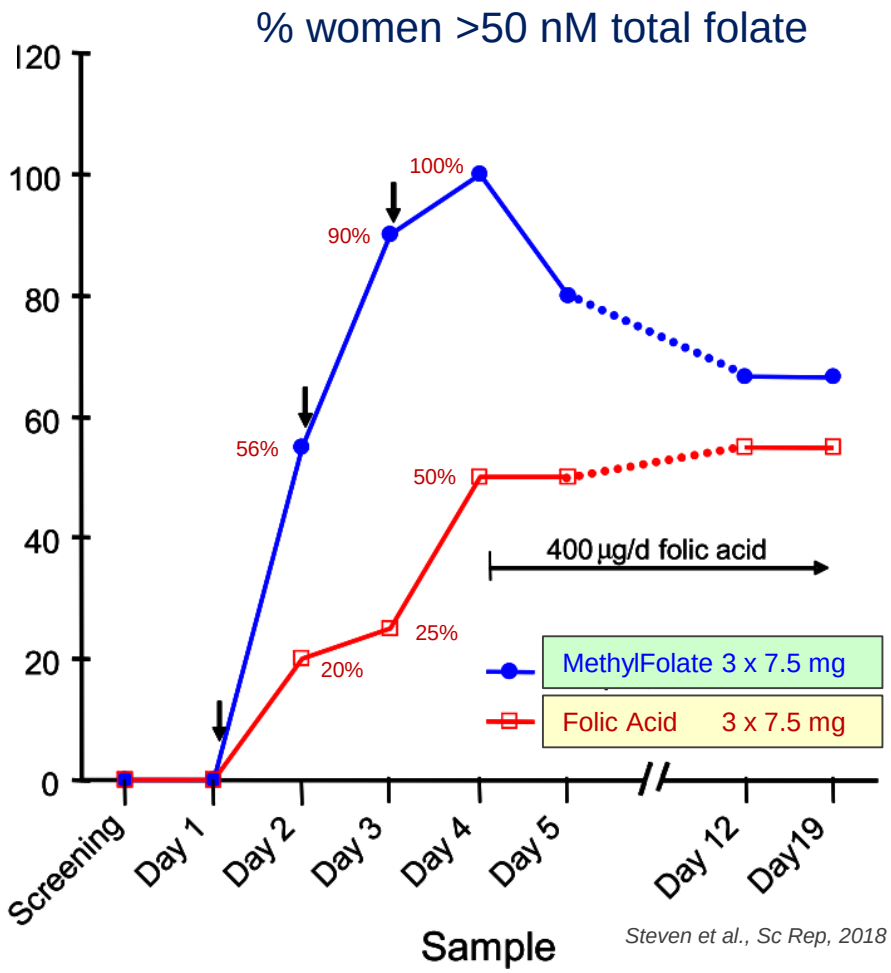
# Somministrazione di MetilFolato o Acido Folico in donne in età fertile




*Steven et al., Sc Rep, 2018*

- La supplementazione con **MetilFolato** è più efficace dell'**Acido Folico** nel migliorare lo stato dei folati serici

# Somministrazione di MetilFolato o Acido Folico in donne in età fertile

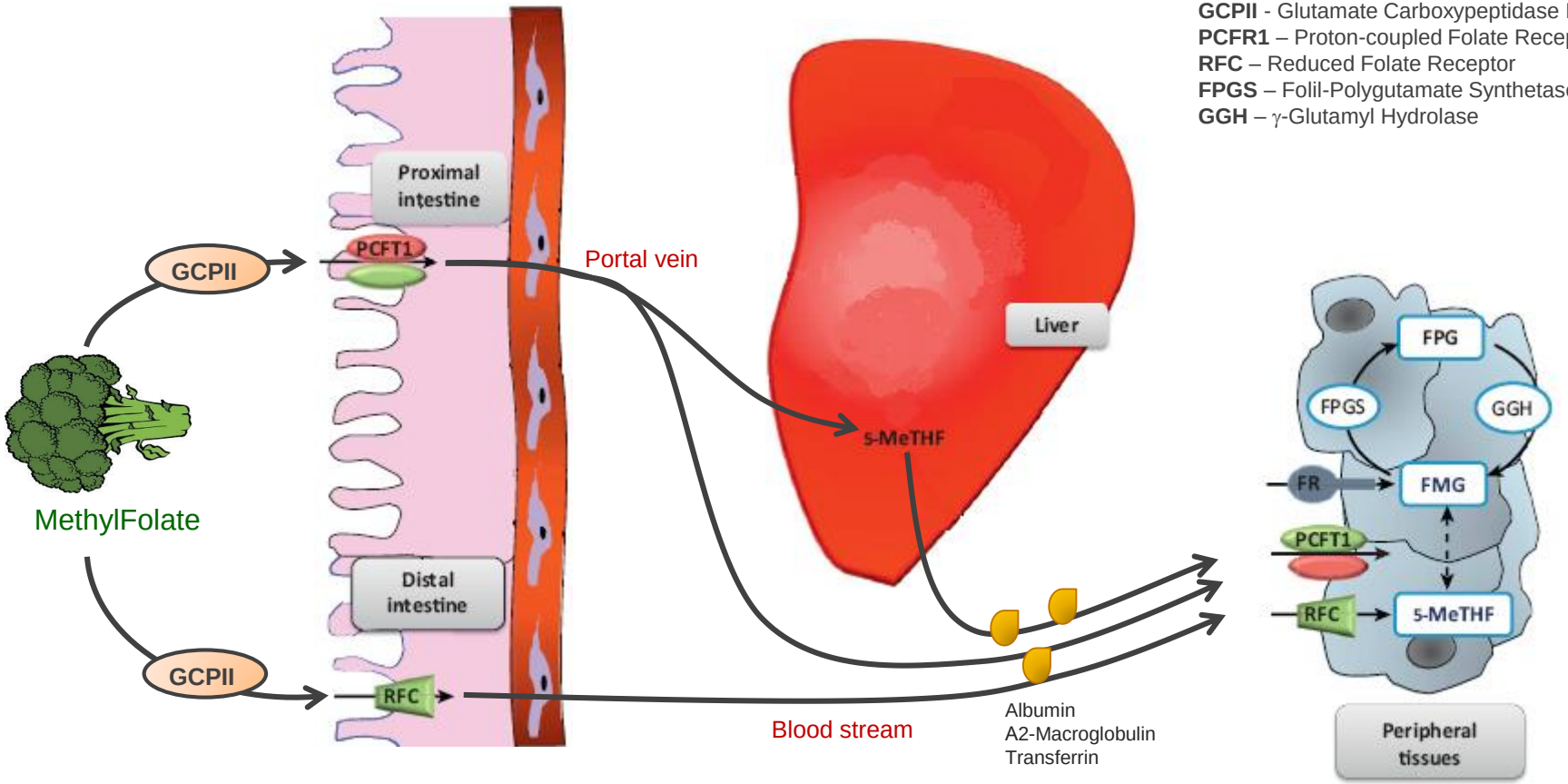



*Steven et al., Sc Rep, 2018*

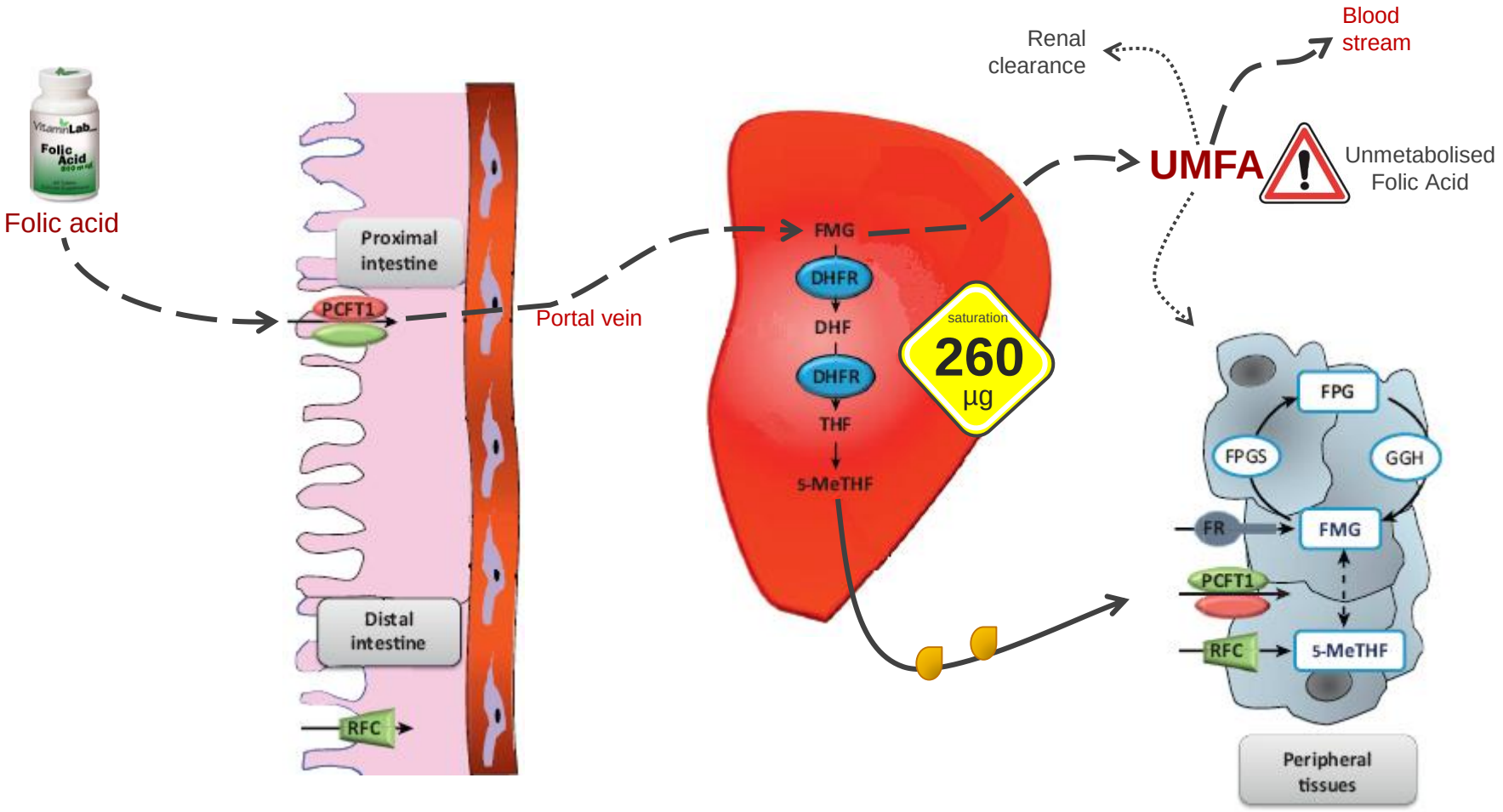
- La supplementazione con **MetilFolato** consente di elevare i folati plasmatici a valori >50 nM nel 90% delle donne in soli due giorni

# Assorbimento e distribuzione dei Folati Naturali

**GCPII** - Glutamate Carboxypeptidase II
**PCFR1** – Proton-coupled Folate Receptor 1
**RFC** – Reduced Folate Receptor
**FPGS** – Folil-Polygutamate Synthetase
**GGH** – γ-Glutamyl Hydrolase



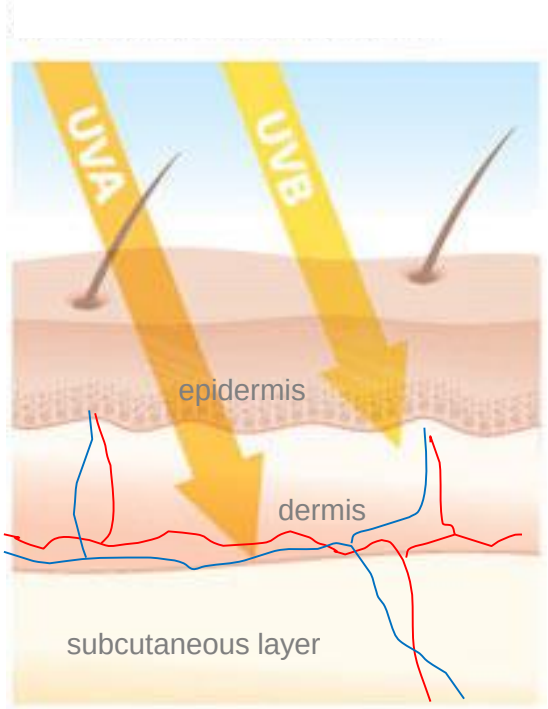
# Assorbimento e distribuzione dell'Acido Folico

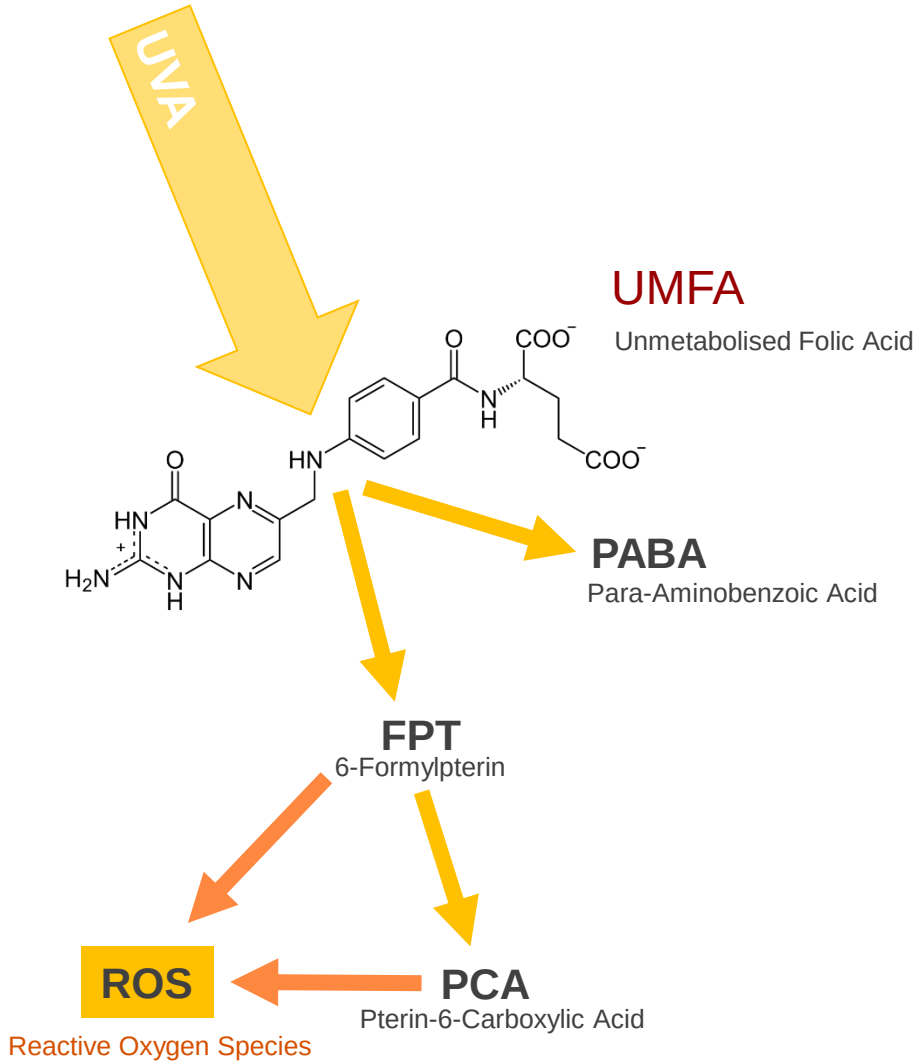



- FA is reduced to MTHF by liver by DHFR at very low rate, due to enzyme saturation (260-280 ug FA)
- 5 mg FA take 12 hours to be converted
- High FA leads to high transient of plasma Unmetabolized FA

- **Unmetabolised FA** may be detrimental:
  - Progression of pre-cancerous lesions
  - Decreased activity of NK cells
  - High FA intake has adverse effects on mouse embryo development (Pickel et al., 2010)

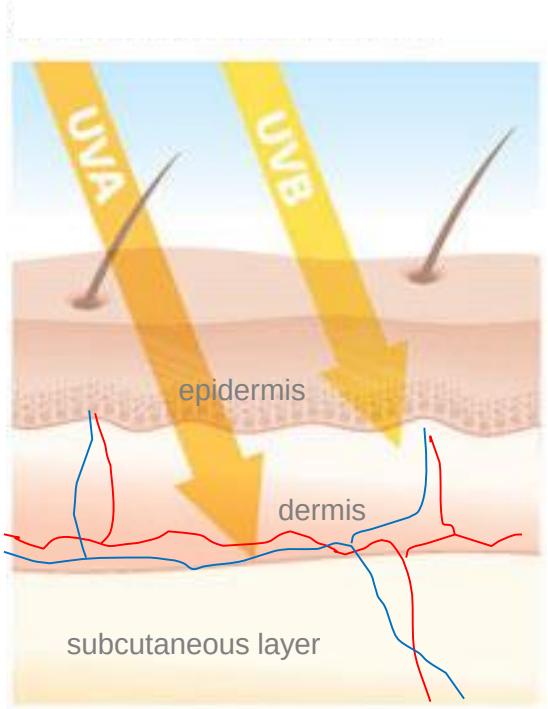
# Fotodegradazione dell'Acido Folico

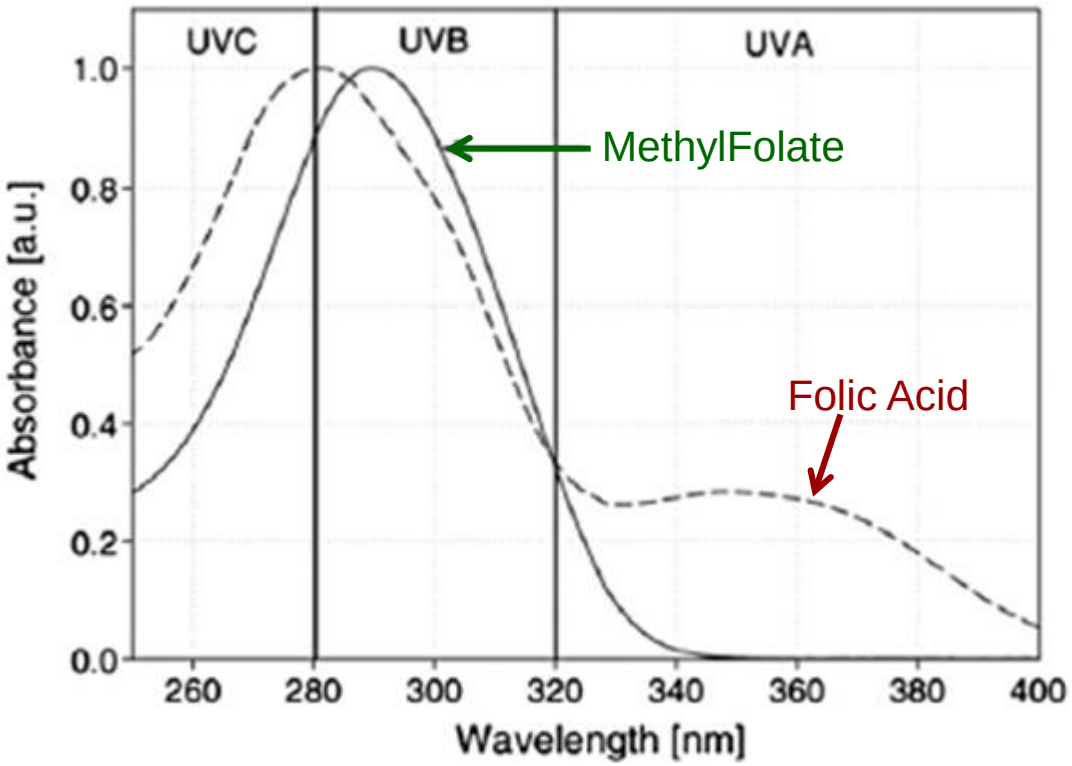



*Michele Rubini, University of Ferrara*

# Fotodegradazione dei Folati



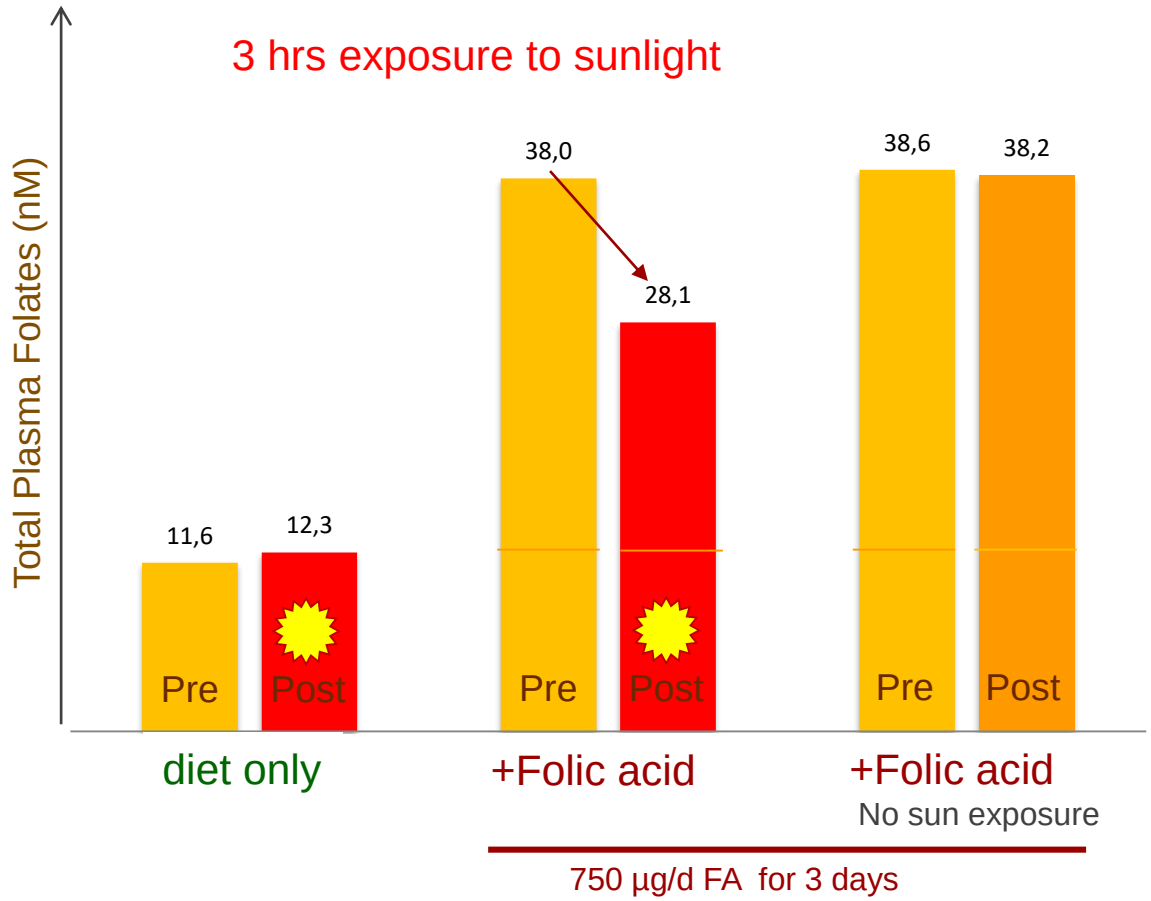




UVA-exposure causes degradation of Folic Acid in the skin vessels

MethylFolate instead is UVA-resistant

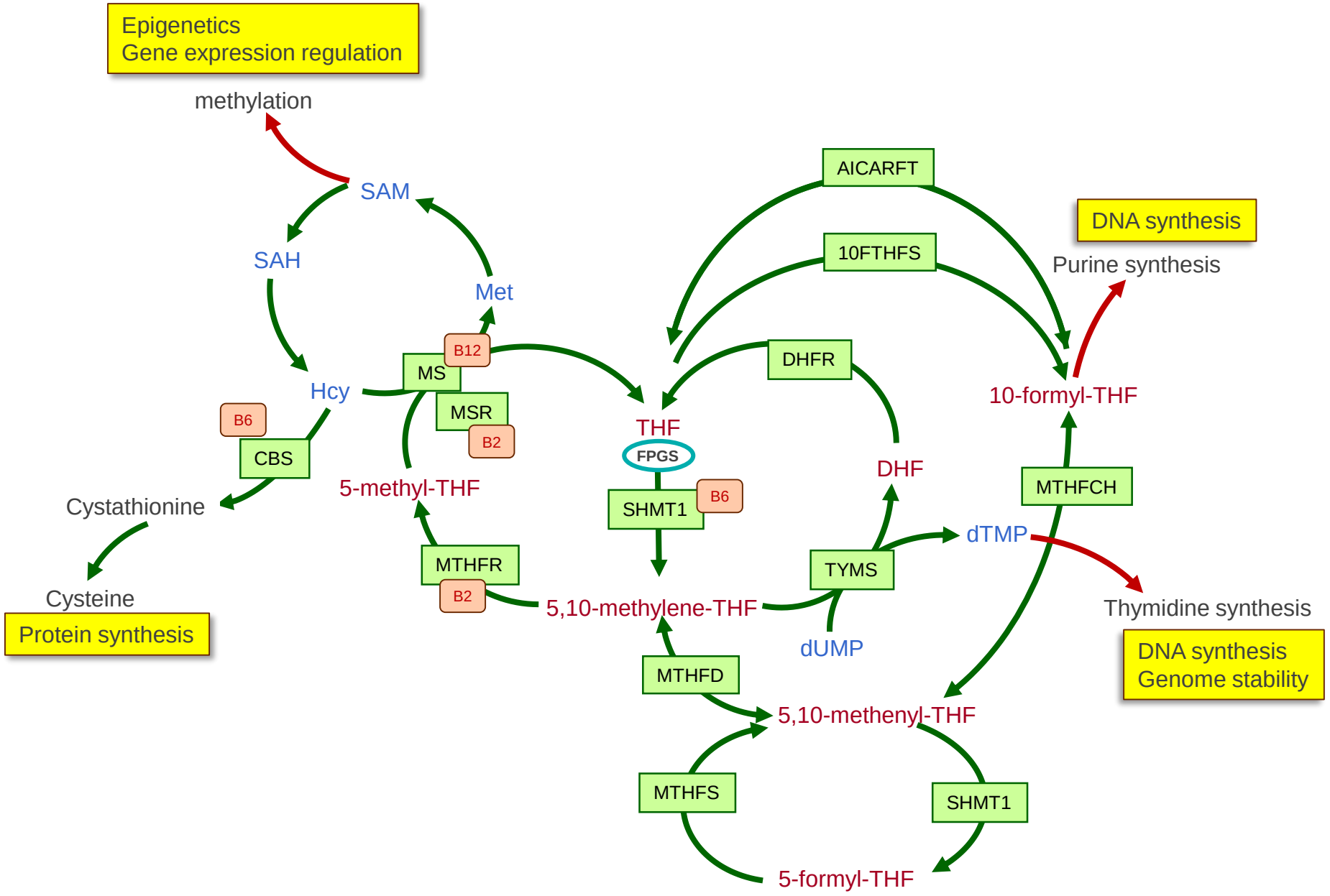
# Fotodegradazione dell'Acido Folico dopo esposizione a luce solare

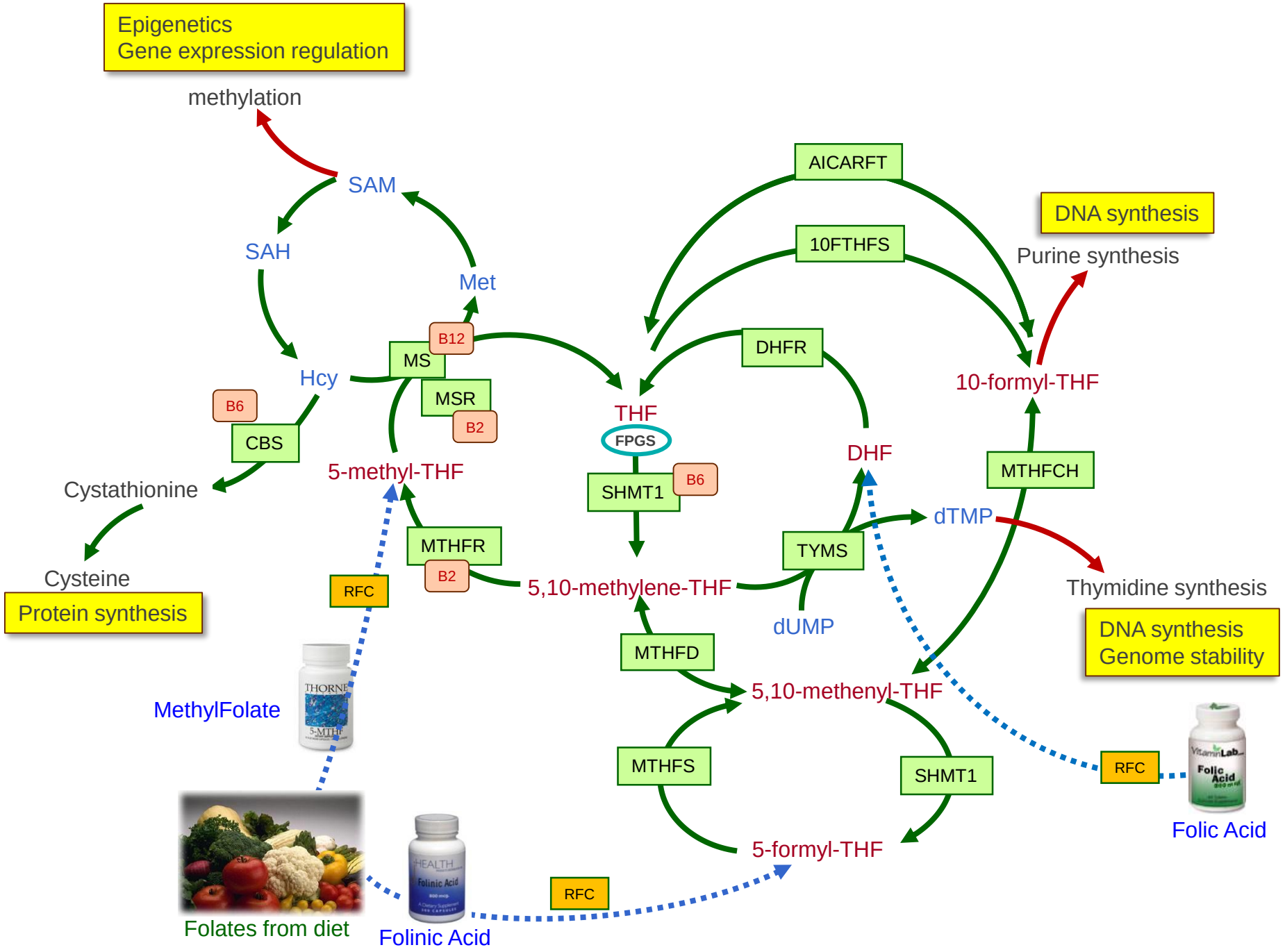
Fukuwatari et al., 2009

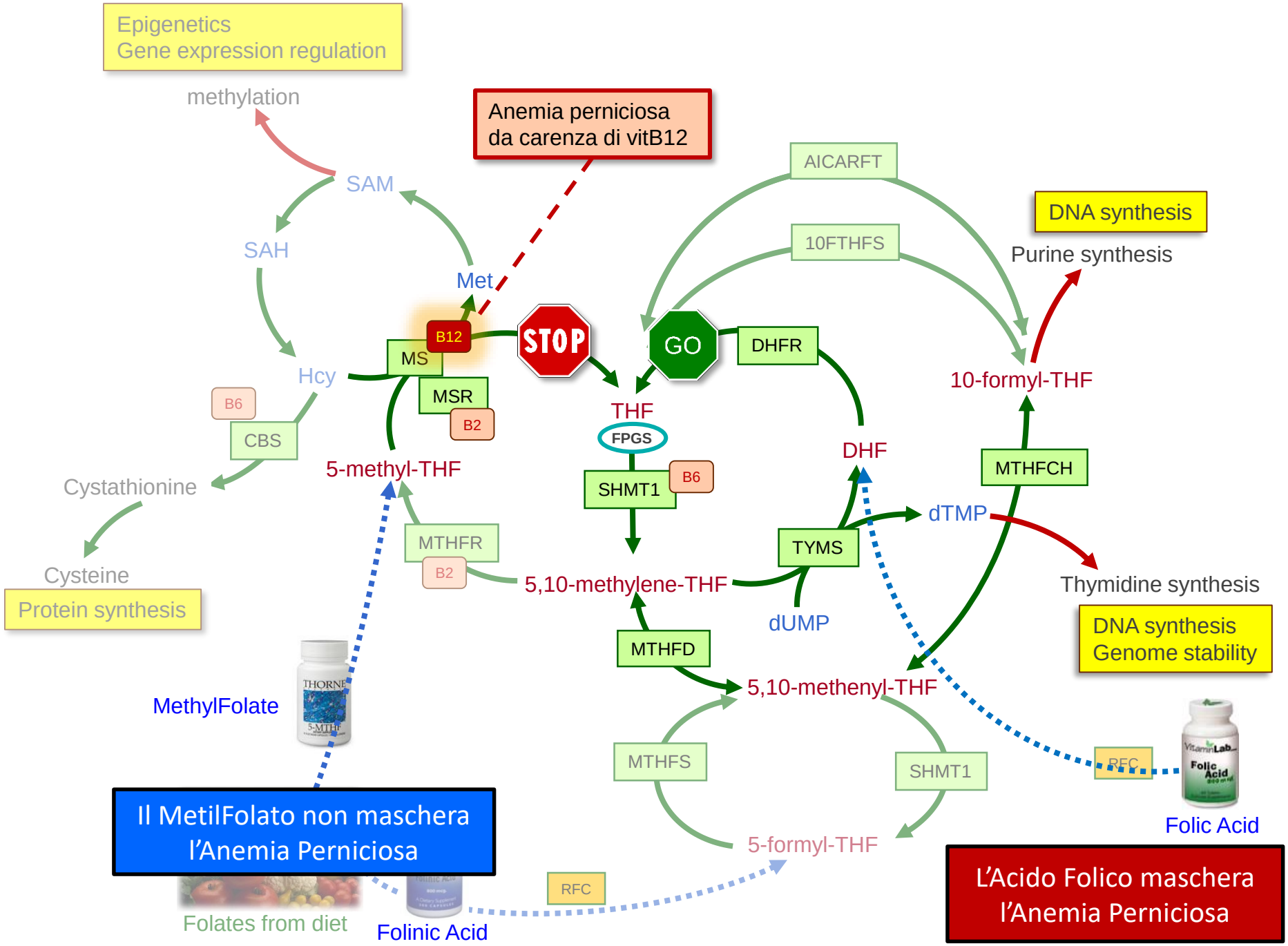


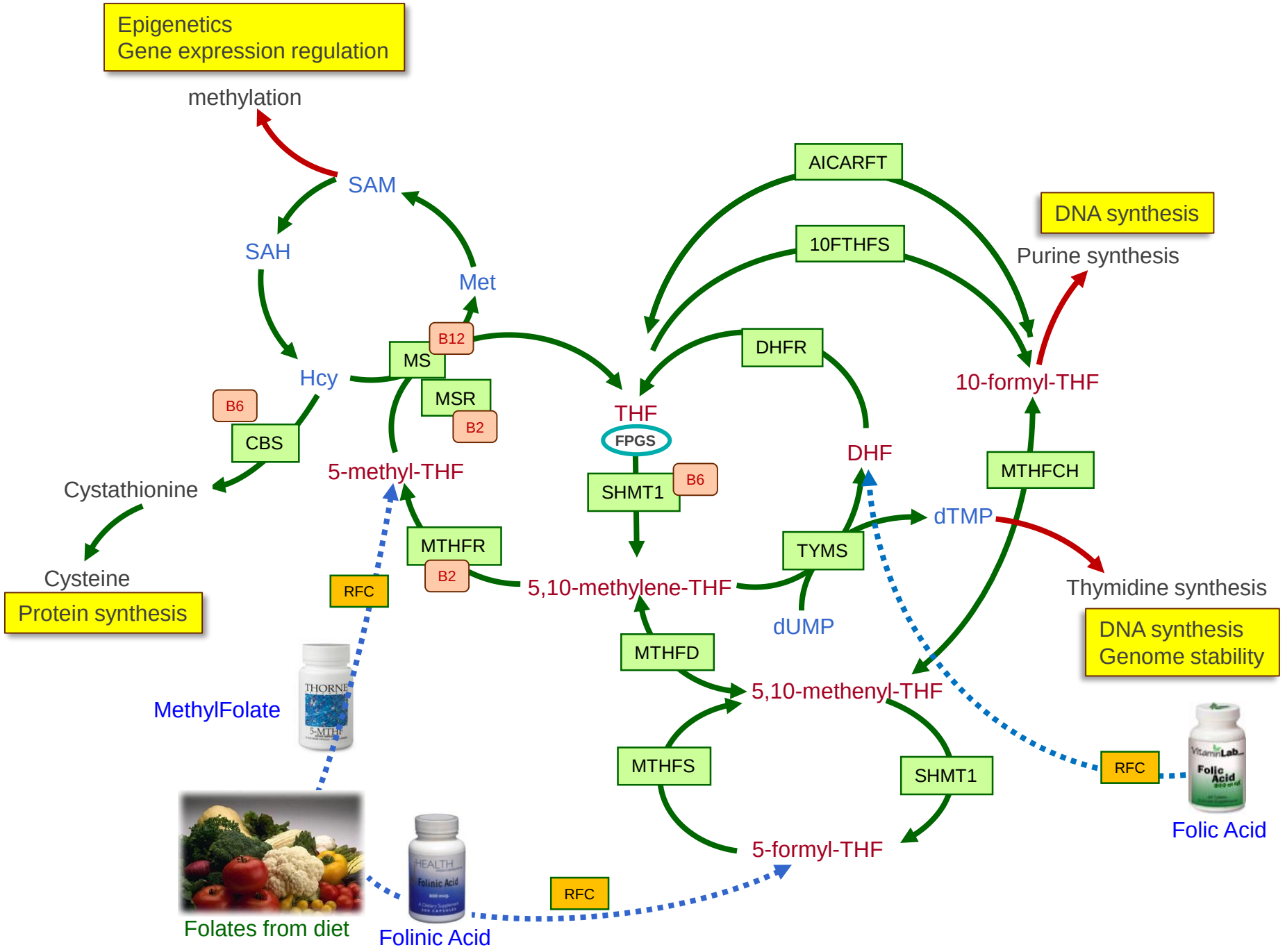

Reduction of plasma folate after sun exposure only in Folic Acid supplemented subjects

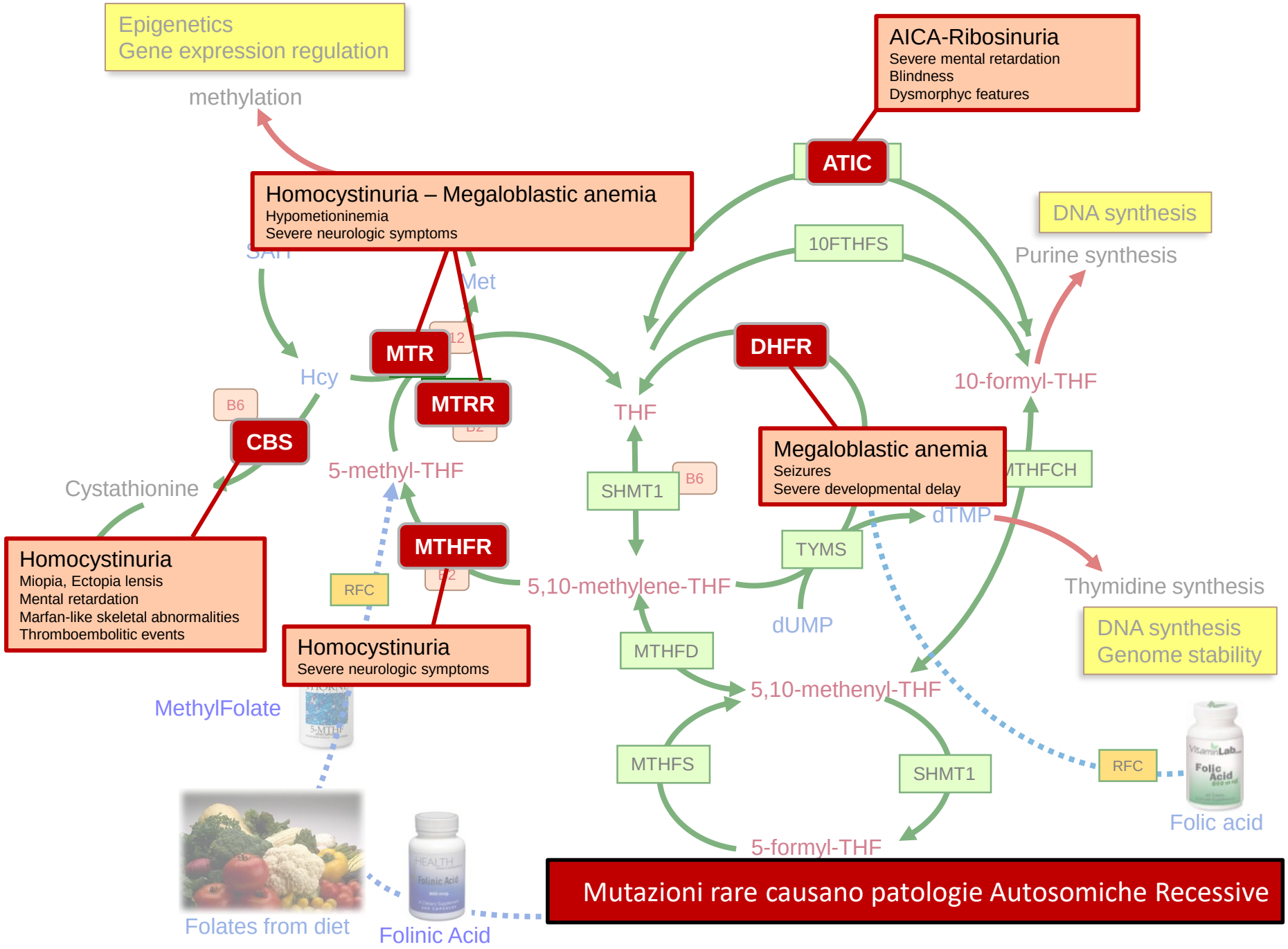
No effect on MethylFolate from diet

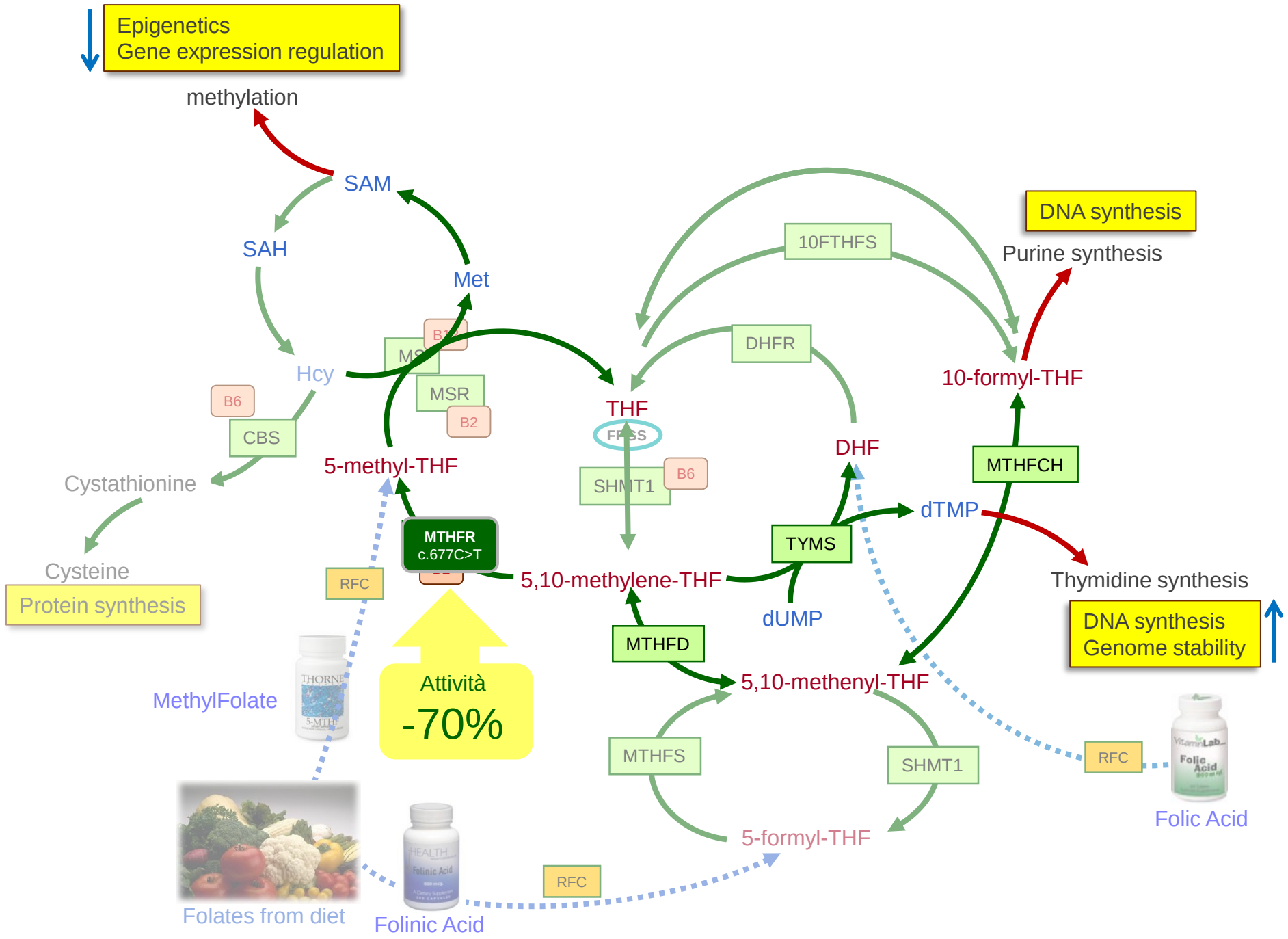

Epigenetics
Gene expression regulation
methylation
SAM
SAH
Met
Hcy
MS
B12
MSR
B2
B6
CBS
Cystathionine
Cysteine
Protein synthesis
5-methyl-THF
MTHFR
B2
5,10-methylene-THF
THF
FPGS
SHMT1
B6
DHFR
DHF
TYMS
dUMP
dTMP
AICARFT
10FTHFS
10-formyl-THF
Purine synthesis
DNA synthesis
MTHFCH
Thymidine synthesis
DNA synthesis
Genome stability
MTHFD
5,10-methenyl-THF
MTHFS
SHMT1
5-formyl-THF

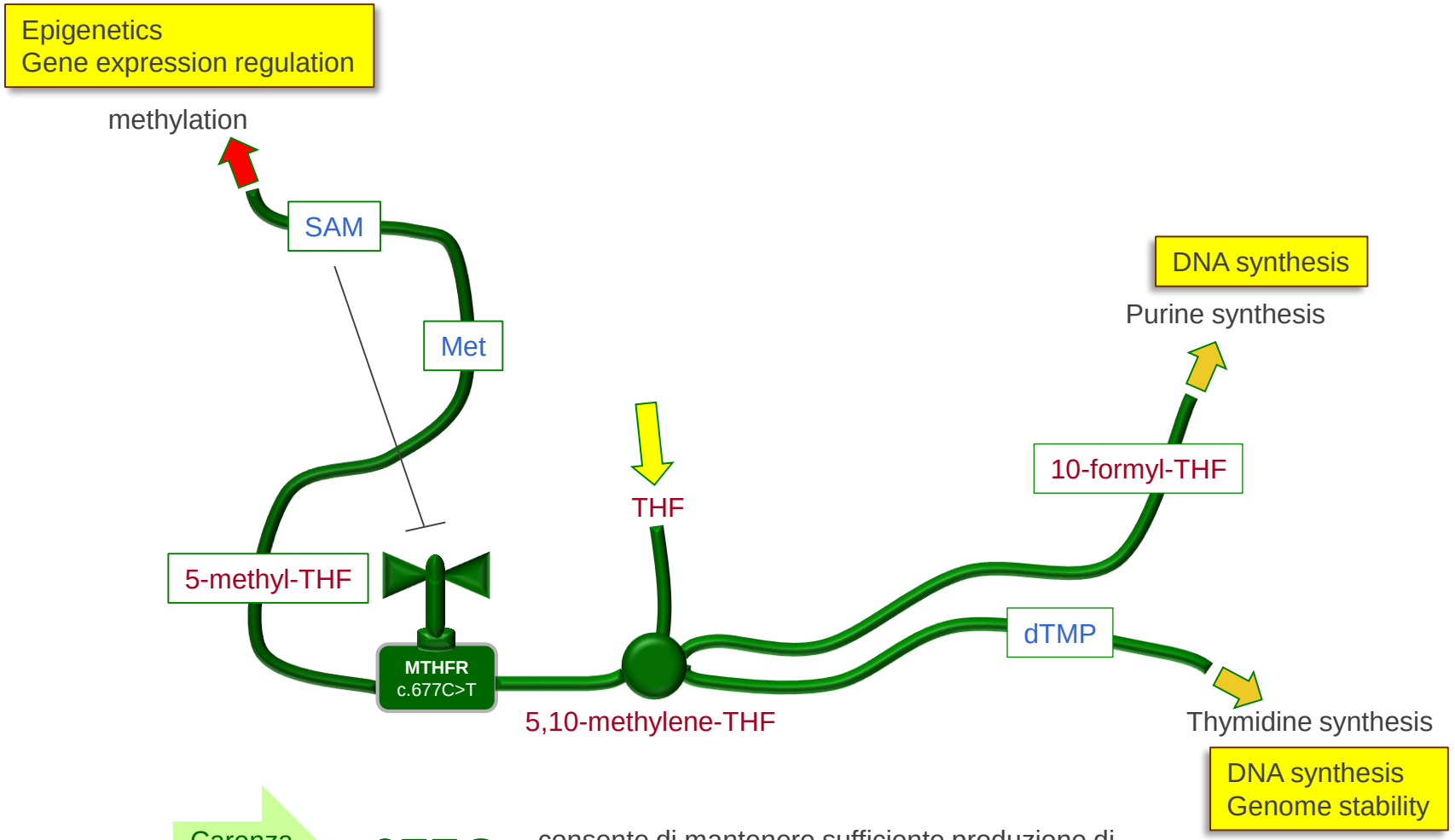

Epigenetics
Gene expression regulation
methylation
SAM
SAH
Met
Hcy
B12
MS
MSR
B2
B6
CBS
Cystathionine
Cysteine
Protein synthesis
5-methyl-THF
MTHFR
B2
RFC
MethylFolate
THORNE
5-MTHF
Folates from diet
HEALTH
Folinic Acid
Folinic Acid
RFC
THF
FPGS
SHMT1
B6
5,10-methylene-THF
MTHFD
5,10-methenyl-THF
MTHFS
SHMT1
5-formyl-THF
AICARFT
10FTHFS
DHFR
DHF
TYMS
dUMP
dTMP
Thymidine synthesis
DNA synthesis
Genome stability
10-formyl-THF
MTHFCH
DNA synthesis
Purine synthesis
RFC
VitaminLab
Folic Acid
Folic Acid


Epigenetics
Gene expression regulation
methylation
SAM
SAH
Hcy
Met
Anemia perniciosa
da carenza di vitB12
B12
MS
MSR
B2
B6
CBS
Cystathionine
Cysteine
Protein synthesis
5-methyl-THF
STOP
GO
THF
FPGS
SHMT1
B6
AICARFT
10FTHFS
DHFR
DHF
DNA synthesis
Purine synthesis
10-formyl-THF
MTHFCH
dTMP
TYMS
dUMP
Thymidine synthesis
DNA synthesis
Genome stability
MTHFR
B2
5,10-methylene-THF
MTHFD
5,10-methenyl-THF
MTHFS
SHMT1
5-formyl-THF
RFC
MethylFolate
Folic Acid
Il MetilFolato non maschera
l'Anemia Perniciosa
Folates from diet
Folinic Acid
RFC
L'Acido Folico maschera
l'Anemia Perniciosa


Epigenetics
Gene expression regulation
methylation
SAM
SAH
Met
Hcy
B12
MS
MSR
B2
B6
CBS
Cystathionine
Cysteine
Protein synthesis
5-methyl-THF
MTHFR
B2
RFC
MethylFolate
THORNE
5-MTHF
Folates from diet
HEALTH
Folinic Acid
Folinic Acid
RFC
THF
FPGS
SHMT1
B6
5,10-methylene-THF
MTHFD
5,10-methenyl-THF
MTHFS
SHMT1
5-formyl-THF
AICARFT
10FTHFS
DHFR
DHF
TYMS
dUMP
dTMP
Thymidine synthesis
DNA synthesis
Genome stability
10-formyl-THF
MTHFCH
DNA synthesis
Purine synthesis
RFC
VitaminLab
Folic Acid
Folic Acid


Epigenetics
Gene expression regulation
methylation
AICA-Ribosinuria
Severe mental retardation
Blindness
Dysmorphyc features
ATIC
Homocystinuria – Megaloblastic anemia
Hypometioninemia
Severe neurologic symptoms
DNA synthesis
10FTHFS
Purine synthesis
SAH
Met
MTR
B12
DHFR
Hcy
10-formyl-THF
B6
MTRR
THF
CBS
5-methyl-THF
Megaloblastic anemia
Seizures
Severe developmental delay
MTHFCH
SHMT1
B6
dTMP
Cystathionine
TYMS
MTHFR
RFC
5,10-methylene-THF
Thymidine synthesis
Homocystinuria
Miopia, Ectopia lensis
Mental retardation
Marfan-like skeletal abnormalities
Thromboembolitic events
dUMP
DNA synthesis
Genome stability
Homocystinuria
Severe neurologic symptoms
MTHFD
5,10-methenyl-THF
MethylFolate
MTHFS
SHMT1
RFC
Folic acid
5-formyl-THF
Folates from diet
Folinic Acid
Mutazioni rare causano patologie Autosomiche Recessive


Epigenetics
Gene expression regulation
methylation
SAM
SAH
Met
Hcy
B6
CBS
Cystathionine
Cysteine
Protein synthesis
B12
MS
MSR
B2
5-methyl-THF
MTHFR
c.677C>T
RFC
THF
FPGS
SHMT1
B6
5,10-methylene-THF
10FTHFS
DHFR
DHF
TYMS
dTMP
dUMP
MTHFD
5,10-methenyl-THF
MTHFS
SHMT1
5-formyl-THF
10-formyl-THF
MTHFCH
DNA synthesis
Purine synthesis
Thymidine synthesis
DNA synthesis
Genome stability
Attività
-70%
MethylFolate
Folates from diet
Folinic Acid
RFC
RFC
Folic Acid

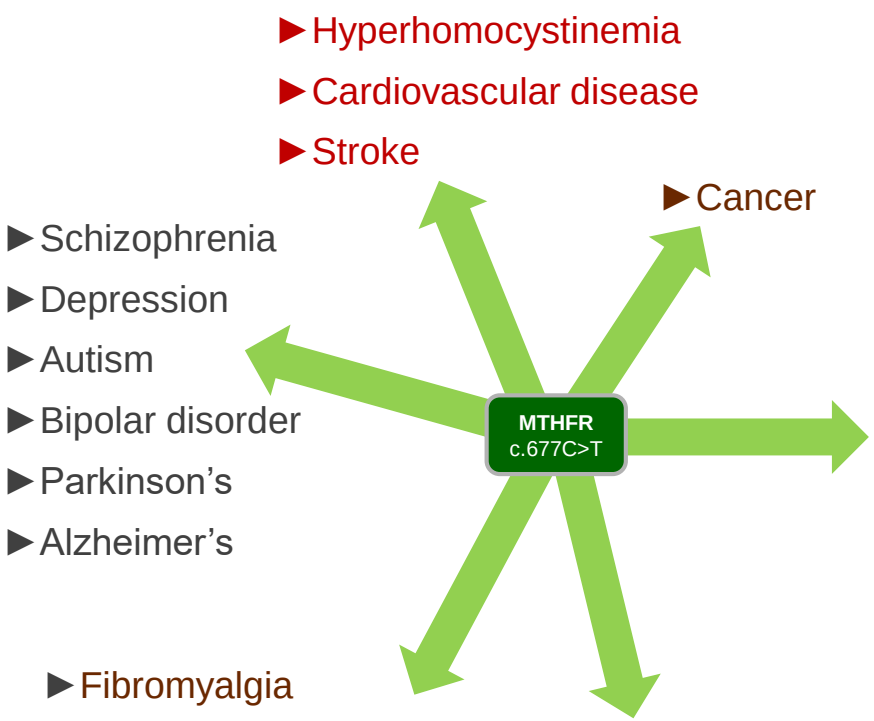



Carenza di folati → **677C** consente di mantenere sufficiente produzione di SAM, indispensabile per lo sviluppo embrionale

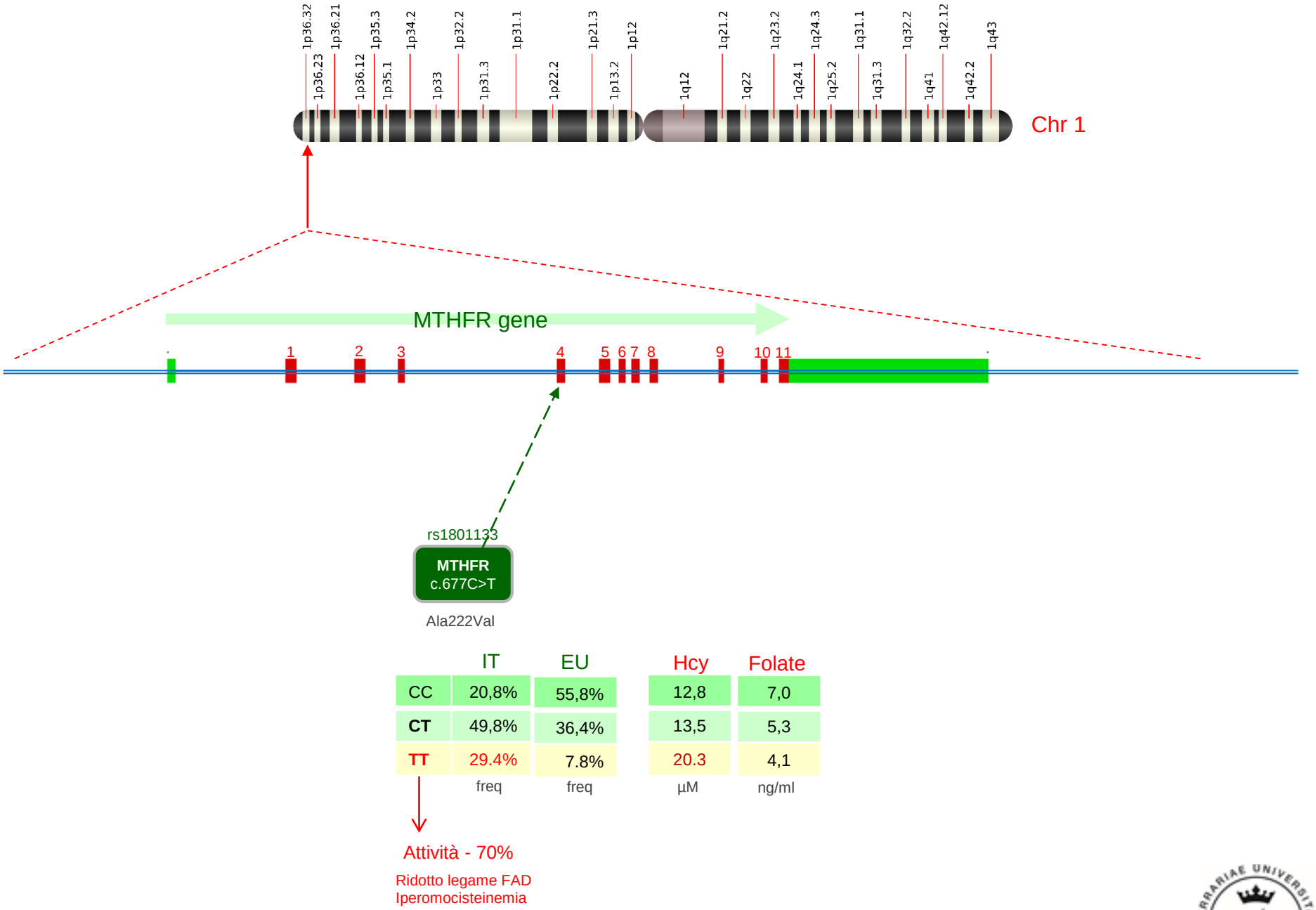
Abbondanza di folati → **677T** favorisce la tutela della stabilità genomica, migliorando ulteriormente la fitness dell'embrione

*Michele Rubini, University of Ferrara*

# Pleiotropia della variante MTHFR:c.677C>T




- Hyperhomocystinemia
- Cardiovascular disease
- Stroke
- Cancer
- Schizophrenia
- Depression
- Autism
- Bipolar disorder
- Parkinson's
- Alzheimer's
- Fibromyalgia
- Chronic fatigue syndrome
- Migraine with aura
- Viral infections
- IBD
- Retinal artery occlusion
- Miscarriage
- Gestational hypertension
- Preeclampsia
- Fetal death
- Neural tube defects
- Orofacial clefts
- Congenital heart defects
- Down syndrome
- Male infertility

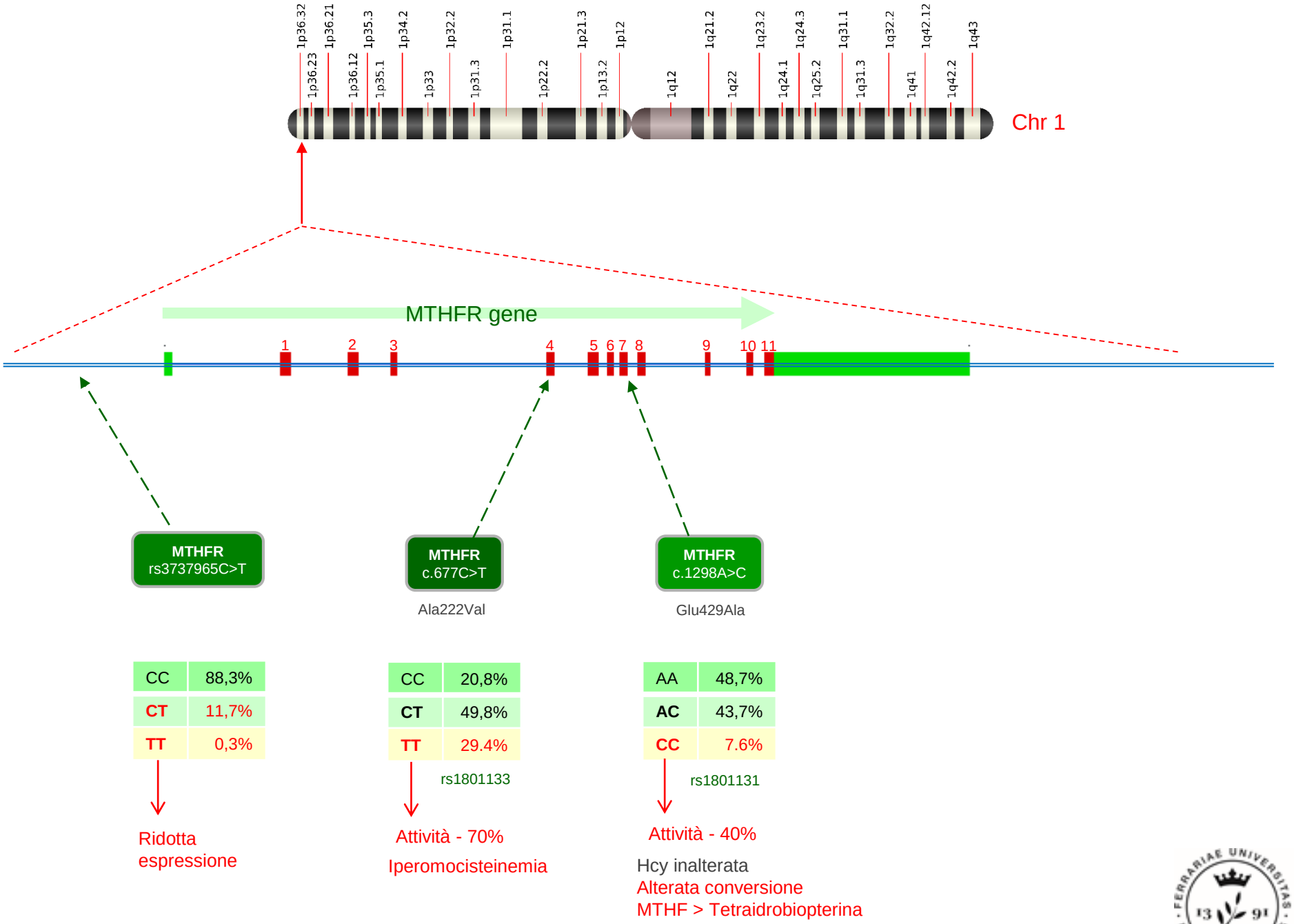



| | IT | EU | Hcy | Folate |
|---|---|---|---|---|
| CC | 20,8% | 55,8% | 12,8 | 7,0 |
| CT | 49,8% | 36,4% | 13,5 | 5,3 |
| TT | 29.4% | 7.8% | 20.3 | 4,1 |
| | freq | freq | µM | ng/ml |

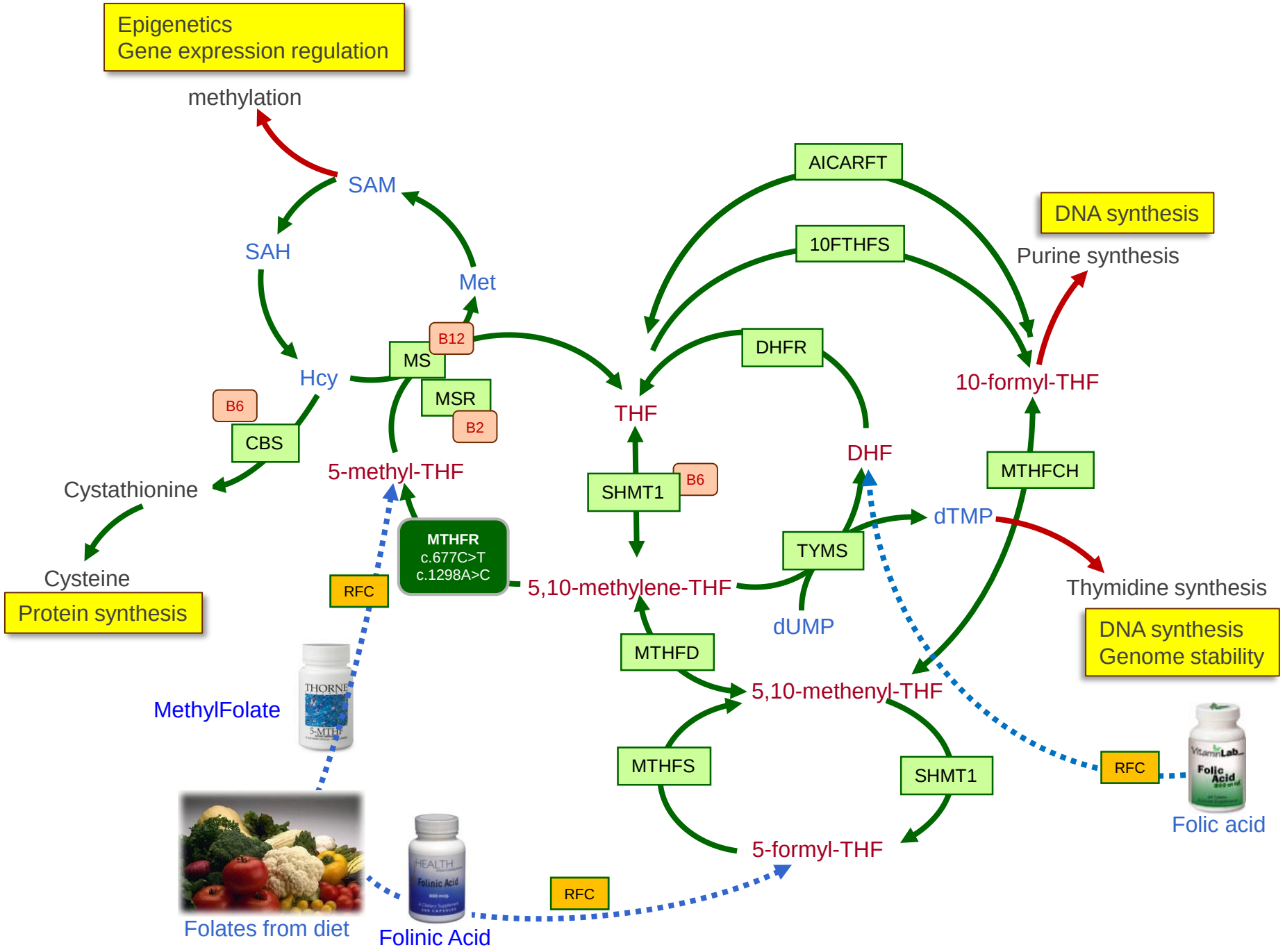
Attività - 70%

Ridotto legame FAD
Iperomocisteinemia

Zappacosta et al., Cell Bioc Funct 2013




*Michele Rubini, University of Ferrara*


Epigenetics
Gene expression regulation
methylation
SAM
SAH
Met
Hcy
B12
MS
MSR
B2
B6
CBS
Cystathionine
Cysteine
Protein synthesis
5-methyl-THF
MTHFR
c.677C>T
c.1298A>C
RFC
MethylFolate
THORNE
5-MTHF
Folates from diet
HEALTH
Folinic Acid
Folinic Acid
RFC
AICARFT
10FTHFS
DNA synthesis
Purine synthesis
DHFR
10-formyl-THF
THF
SHMT1
B6
DHF
MTHFCH
dTMP
TYMS
5,10-methylene-THF
dUMP
Thymidine synthesis
DNA synthesis
Genome stability
MTHFD
5,10-methenyl-THF
MTHFS
SHMT1
5-formyl-THF
RFC
VitaminLab
Folic Acid
Folic acid

Epigenetics
Gene expression regulation

# Polimorfismi comuni condizionano il bilancio complessivo dei folati

methylation

SAM

SAH

Met

Hcy

B6

CBS
c.844ins68

Cystathionine

Cysteine

Protein synthesis

MTR
c.2756A>G

MTRR
c.66G>A

5-methyl-THF

SLC19A1
c.80G>A

MTHFR
c.677C>T
c.1298A>C

MethylFolate

Folates from diet

Folinic Acid

SLC19A1
c.80G>A

THF

SHMT1
c.1420C>T

B6

ATIC
c.347C>G

MTHFD1
c.1258G>A

DHFR
19bp del I>D

DHF

TYMS
28bp 3>2
6bpdel I>D

5,10-methylene-THF

dUMP

MTHFD1
c.1258G>A

5,10-methenyl-THF

MTHFS
c.604A>G
rs622506T>G

SHMT1
c.1420C>T

5-formyl-THF

DNA synthesis

Purine synthesis

10-formyl-THF

MTHFD1
c.1258G>A

dTMP

Thymidine synthesis

DNA synthesis
Genome stability

SLC19A1
c.80G>A

Folic acid

# Polimorfismi dei folati associati a rischio di NTD

Epigenetics
Gene expression regulation

methylation

SAM

SAH

Met

Hcy

B12

MS

MTRR
c.66G>A

B6

CBS
c.844ins68

Cystathionine

Cysteine

Protein synthesis

5-methyl-THF

MTHFR
c.677C>T
c.1298A>C

SLC19A1
c.80G>A

AICARFT

MTHFD1
c.1258G>A

DNA synthesis

Purine synthesis

DHFR
19bp del I>D

10-formyl-THF

THF

FPGS

SHMT1

B6

DHF

MTHFD1
c.1258G>A

TYMS
28bp 3>2
6bpdel I>D

dTMP

Thymidine synthesis

5,10-methylene-THF

dUMP

DNA synthesis
Genome stability

MTHFD1
c.1258G>A

5,10-methenyl-THF

MTHFS

SHMT1

5-formyl-THF

SLC19A1
c.80G>A

Folic Acid

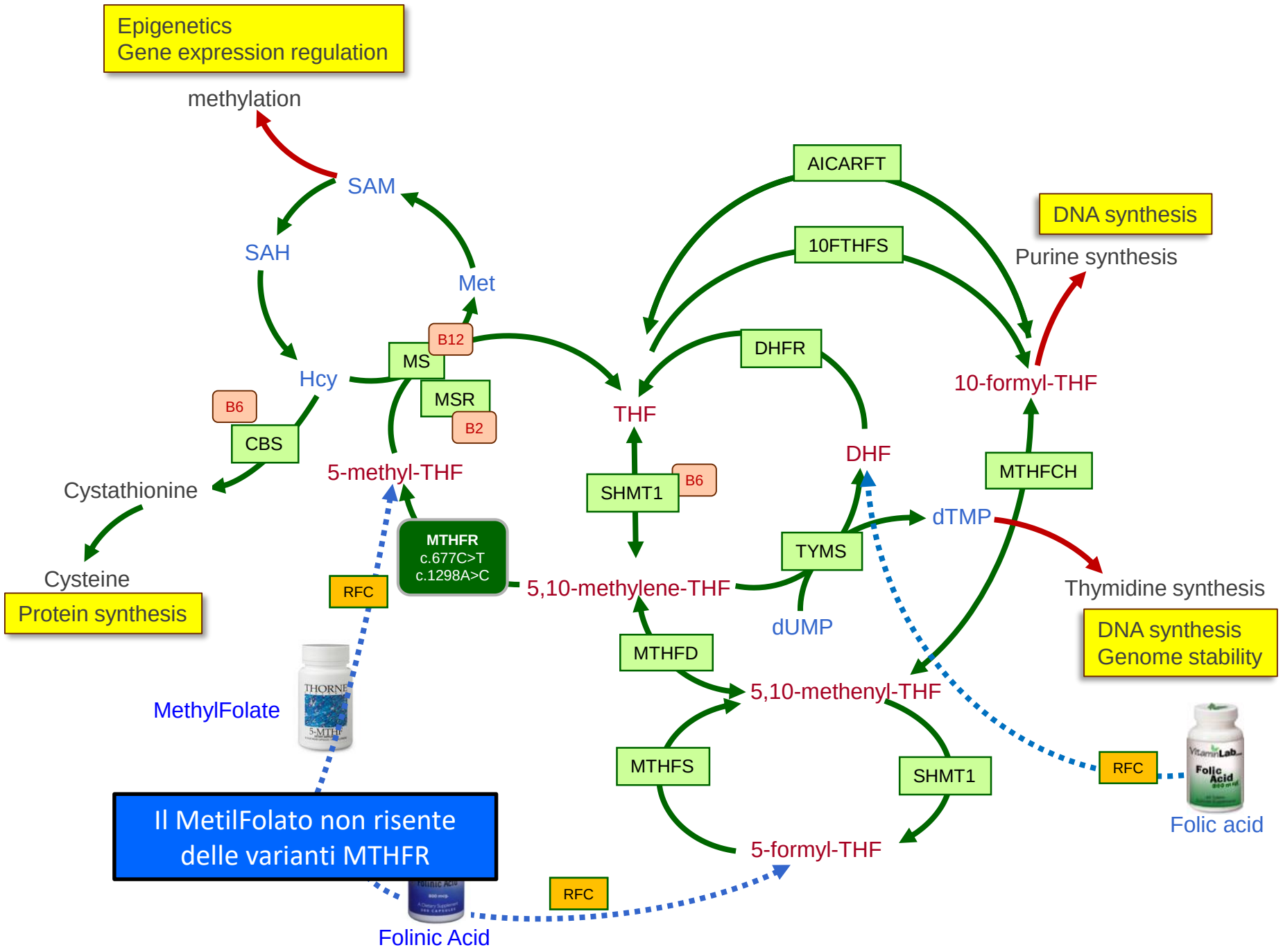
Solo MTHFR 677C>T risulta replicato in studi indipendenti

Folates from diet

Folinic Acid

SLC19A1
c.80G>A

Au et al., 2010


Epigenetics
Gene expression regulation
methylation
SAM
SAH
Met
Hcy
B12
MS
MSR
B2
B6
CBS
Cystathionine
Cysteine
Protein synthesis
5-methyl-THF
MTHFR
c.677C>T
c.1298A>C
RFC
MethylFolate
Il MetilFolato non risente
delle varianti MTHFR
Folinic Acid
RFC
AICARFT
10FTHFS
DNA synthesis
Purine synthesis
DHFR
10-formyl-THF
THF
SHMT1
B6
DHF
MTHFCH
dTMP
TYMS
5,10-methylene-THF
dUMP
Thymidine synthesis
DNA synthesis
Genome stability
MTHFD
5,10-methenyl-THF
MTHFS
SHMT1
5-formyl-THF
RFC
Folic acid


UV

Photodegradation


Folic acid

ROS

UMFA

Adverse Effects (?)

PABA+Pteridine

**DHFR**
19bp del I>D

DHF

**DHFR**
19bp del I>D


Folinic Acid

THF

**MTHFR**
c.677C>T
c.1298A>C


MethylFolate

Diet

**MethylFolate**

Active form of Folate

SAM

**Epigenomics**

NO

**Anti-Oxydant**

Aa DNA

**Cell prolipheration**

TMP

**Genome stability**

# MethylFolate


Promptly bioavailable

Better pharmacokinetics

Lower urinary excretion

NO UMFA

NO UV-degradation

NO genotype-dependent

Lower B12-deficiency masking


Unità di Epidemiologia Genomica e Farmacogenetica

Dip. Scienze Biomediche e Chirurgico-Specialistiche
Università degli Studi di Ferrara