

# **GUILD Conference 2022** February 20-23

Wailea Marriott • Maui, Hawaii



## Disclosures

• Consultant for Freenome Inc and Iterative Scopes

## Outline

- Principles of Chemoprevention
- Historical perspective
- Evidence review Supplemental agents for Cancer and CRC
- Best Practice Advice

## Introduction

-Single cancer

-Too late or too difficult

- Diet vs. supplement

#### Approach

- Anatomic
- Public Health
- Metabolic

#### Mechanism

- Remove adenoma
- Remove carcinogen
- Chemoprevention

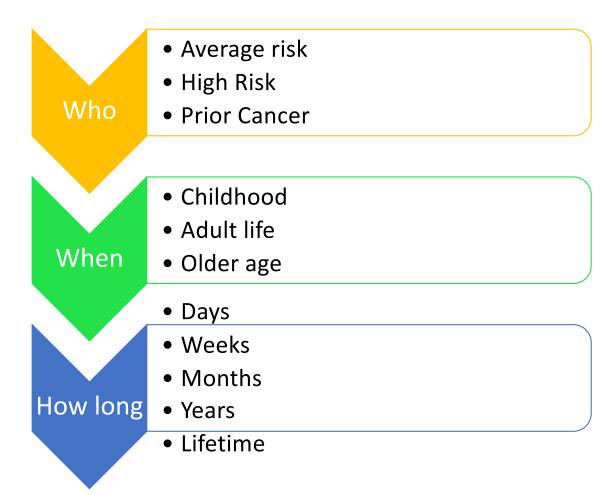
#### Examples

- Colon adenomas
- Smoking Cessation

# Big Picture







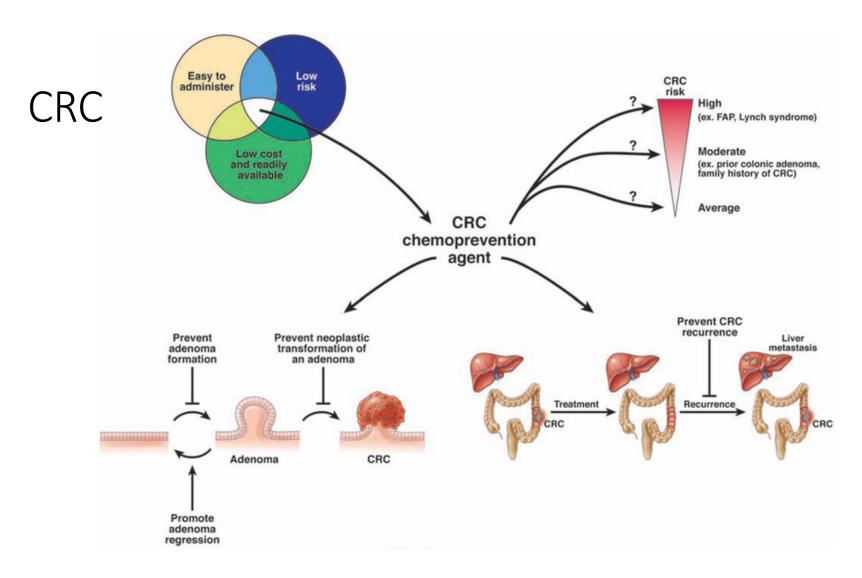
## Historical

| Cardiovascular event                                 | Colorectal cancer   |
|--|---|
| Measurement of systolic and diastolic blood pressure | 1900s   |
| Wide prevalence of blood pressure monitors           | 1930s   |
| Usefulness of blood pressure as a biomarker          | 1970s   |
| Usefulness of serum cholesterol as a biomarker       | 1980s   |
| Preventive effect of aspirin in RCTs                 | Adenoma-carcinoma sequence in CRC                                       |
| Preventive effect of statins in RCTs                 | 1990s<br>CRC reduction by endoscopic polypectomy                        |
|  | Usefulness of ACF as a surrogate marker of CRC<br>2000s RCTs of calcium |
| Preventive effect of EPA in RCTs                     | Aspirin prevented adenomas in RCTs Coxibs prevented adenomas in RCTs    |
|  | 2010s   |
|  | Metformin prevented adenomas in a RCT                                   |

Umezawa S, Higurashi T, Komiya Y, et al. Chemoprevention of colorectal cancer: Past, present, and future. *Cancer Sci.* 2019;110(10):3018-3026.

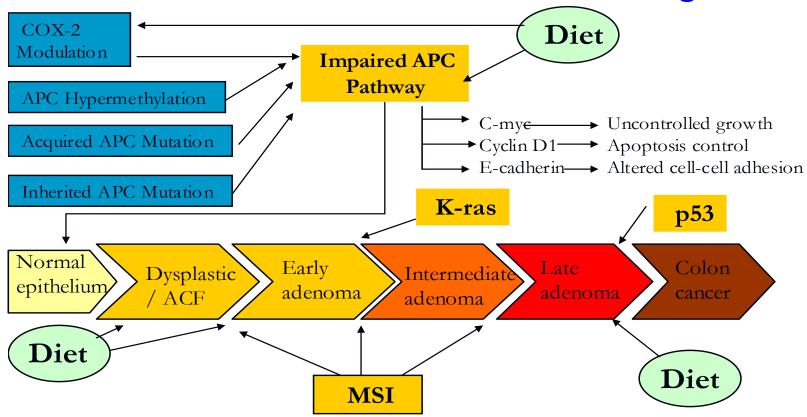
# Late 20<sup>th</sup> century Chemoprevention candidates

|                 | CVD         | Cancer      |
|-----------------|-------------|-------------|
| B-Carotene      | Harmful     | Harmful     |
| Vitamin C and E | Didn't work | Didn't Work |
| Folic Acid      | Didn't work | Didn't work |
| ASA             | Beneficial  | Beneficial  |



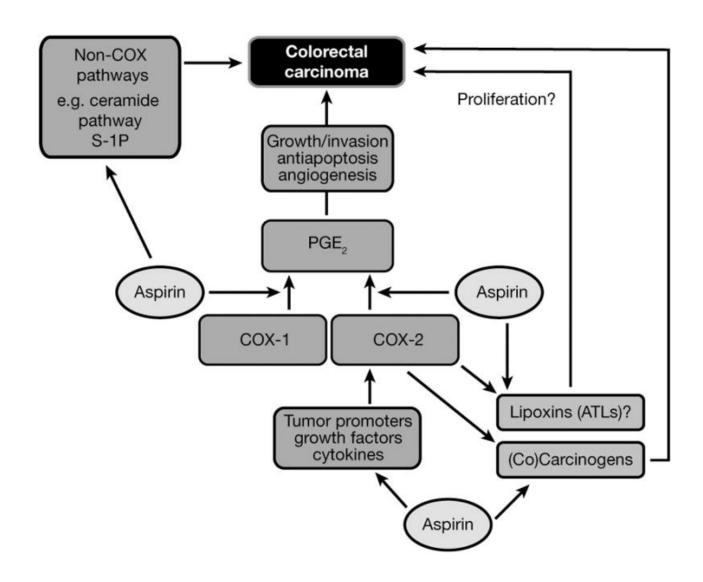
Katona BW, Weiss JM. Chemoprevention of Colorectal Cancer. Gastroenterology. 2020;158(2):368-388

### **Molecular Basis of Colon Carcinogenesis**

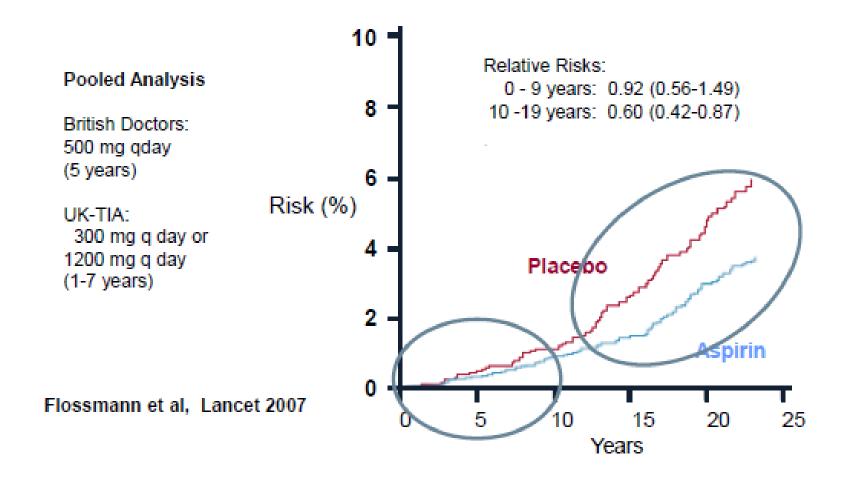


Modified from Vogelstein B, Knizler KW. The multi-step nature of cancer. Trends Genet 1993; 9:138-141.

## ASA

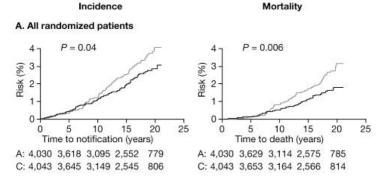


# Aspirin for CRC

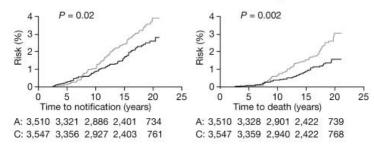


## ASA and CRC Risk

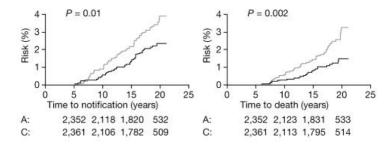
Chan AT, et al. Aspirin in the chemoprevention of colorectal neoplasia: an overview. Cancer Prev Res (Phila). 2012 Feb;5(2):164-78.



#### B. Patients with scheduled duration of trial treatment ≥ 2.5 years



#### C. Patients with scheduled duration of trial treatment ≥ 5 years



## Risk Benefit Ratio

Hypothetical Example: Population of 100,000 Risk=1.5 per 1000 cases/year\*

\*Colorectal cancer risk in US males, aged 65-69 years

- Effective agent: ↓ 50% of CRC after 5 years
- Safe: annual risks of 0.01% stroke, 0.1% GI bleed
- Other benefit: prevents MI 0.1% per year
- Over 10 years: 375 CRC
  - 1000 MI's
  - +100 strokes
  - +1000 GI bleeds

Net: ???

#### Off target effects matter

- Toxicity can negate an "effective" agent.
- Non-colorectal benefits may be needed for effectiveness

### **Annals of Internal Medicine**



www.USPreventiveServicesTaskForce.org

| Population     | Adults aged 50 to 59 y with a ≥10% 10-y CVD risk | Adults aged 60 to 69 y with a ≥10% 10-y CVD risk                              | Adults younger than 50 y | Adults aged 70 y or older                              |
|----------------|--|---|--------------------------|--|
| Recommendation | Initiate low-dose aspirin use.<br>Grade: B       | The decision to initiate low-dose aspirin use is an individual one.  Grade: C | No recommendation        | No recommendation.<br>Grade: I (insufficient evidence) |

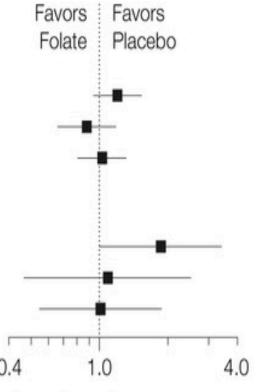
| Population   | Recommendation 2021  | <u>Grade</u> |
|--|--|--------------|
| Adults ages 40 to 59 years with a 10% or greater 10-year cardiovascular disease (CVD) risk | Individualize decision   | C            |
| Adults age 60 years or older   | The USPSTF recommends against initiating low-dose aspirin use for the primary prevention of CVD in adults age 60 years or older. | D            |

Bibbins-Domingo etal. AIM 2016 Jun 21;164(12):836-45.

## ASA and Folic Acid for CRC Precursor lesions: RCT

#### • N=1409

| Adenomas, No./Total No. (%) of Patients |  |  |
|---|--|--|
| Folate                                  | Placebo  |  |
| 87/168 (51.8)                           | 70/162 (43.2)  |  |
| 58/168 (34.5)                           | 65/166 (39.2)  |  |
| 76/165 (46.1)                           | 71/158 (44.9)  |  |
|   |  |  |
| 27/168 (16.1)                           | 14/162 (8.6)   |  |
| 11/168 (6.5)                            | 10/166 (6.0)   |  |
| 19/165 (11.5)                           | 18/158 (11.4)  |  |
|   | Folate<br>87/168 (51.8)<br>58/168 (34.5)<br>76/165 (46.1)<br>27/168 (16.1)<br>11/168 (6.5) |  |



Risk Ratio (95% Confidence Interval)

Cole BF et al. JAMA. 2007;297(21):2351-2359

## Calcium and Vitamin D

Vitamin D
Serum 25-(OH)D & Colorectal Cancer Risk

2.00 P trend < .001

1.00

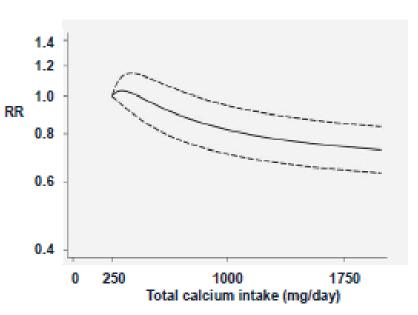
0.50

20 40 60 80 100 120

Circulating 25(OH) D, in nmol/L

Calcium

Total Calcium Intake & Colorectal Cancer Risk



McCullough et al. JNCI 2019 Keum et al, Int J Cancer 2014

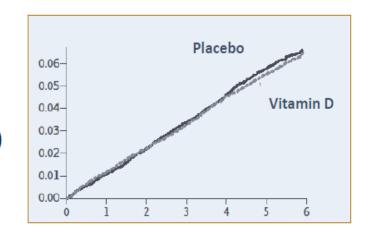
### Supplemental Vitamin D and Calcium for Cancer and CRC

#### Vitamin D Trial (VITAL)

25871 subjects 2000 IU Vitamin D<sub>3</sub> vs placebo

All Cancer HR=0.96 (0.88-1.06)

Colorectal Cancer HR=1.09 (0.73-1.62) (98 events)

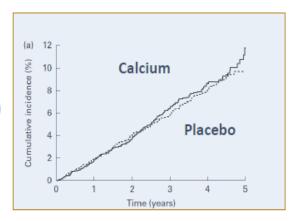


Manson et al. NEJM 2019 3;380(1):33-44 Bristow et al Br J Nutr 2013;110(8):1384-93

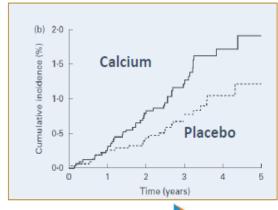
#### Calcium Trial Combined Analysis:

5 trials 7221 subjects 0.6 – 1.0 gm Ca<sup>++</sup>

All Cancer HR=1.07 (0.89, 1.28) 448 cases

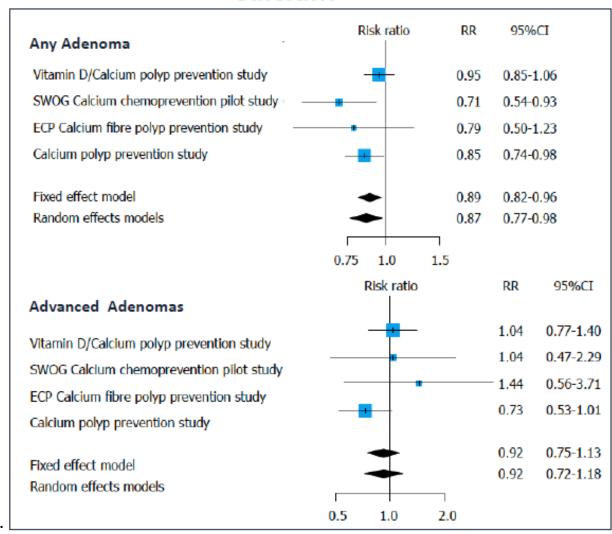


Colorectal Cancer HR=1·63 (1·01, 2·64) 70 cases



#### Calcium

Calcium Supplementation for Adenoma recurrence



Shaukat A et al. AJG 2005;100(2):390-4.

Can Calcium Chemoprevention of Adenoma Recurrence Substitute for Colonoscopic Surveillance or Extend Surveillance Intervals?

## Cost Effectiveness Analysis



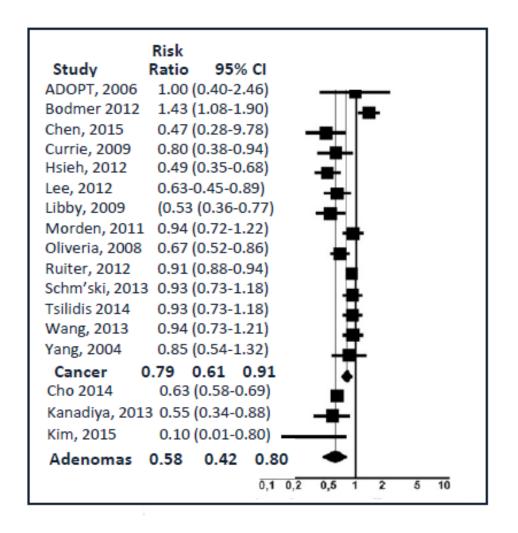
Shaukat A, Parekh M, Lipscomb J, Ladabaum U. Can calcium chemoprevention of adenoma recurrence substitute or serve as an adjunct for colonoscopic surveillance? Int J Technol Assess Health Care. 2009;25(2):222-31

## Cost effectiveness of Calcium supplementation

|                           | Life years per<br>person | Cost per<br>person | Life years<br>gained in a<br>cohort of 1000<br>people (vs.<br>NH) |
|---------------------------|--------------------------|--------------------|---|
| Natural<br>History (NH)   | 18.6424                  | \$2,450            | 0.0   |
| Calcium                   | 18.6543                  | \$2,350            | 11.9  |
| Surveillance              | 18.7289                  | \$4,003            | 86.5  |
| Calcium +<br>Surveillance | 18.7292                  | \$4,118            | 86.8  |

Shaukat A, Parekh M, Lipscomb J, Ladabaum U. Can calcium chemoprevention of adenoma recurrence substitute or serve as an adjunct for colonoscopic surveillance? Int J Technol Assess Health Care. 2009;25(2):222-31

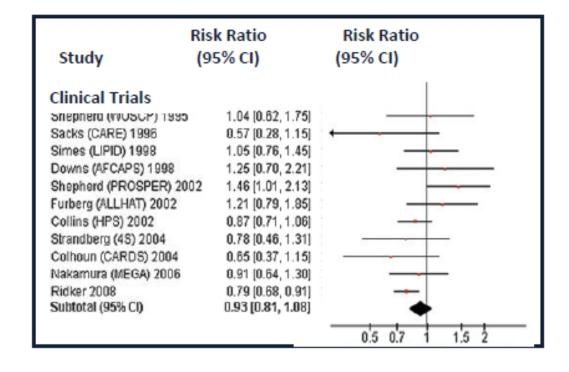
# Metformin



Rokkas et al. Eur J Int Med 2016

## Statins and CRC Risk

Bardou et al Gut 2010



# All together

Events Total Events Total Weight M-H, Random, 95% CI Year M-H, Random, 95% CI Study or Subgroup 1.1.1 Metformin 0.42 [0.21, 0.85] 2016 Higurashi 2016 22 71 62 4.5% Subtotal (95% CI) 71 62 4.5% 0.42 [0.21, 0.85] Total events 22 32 Heterogeneity: Not applicable Test for overall effect: Z = 2.40 (P = .02)1.1.2 Non-aspirin NSAIDs Arber 2006 95 589 83 334 8.2% 0.58 [0.42, 0.81] 2006 Baron 2006 460 1158 646 1218 9.8% 0.58 [0.50, 0.69] 2006 Bertagnolli 2006 548 1356 421 679 9.6% 0.42 [0.34, 0.50] 2006 Subtotal (95% CI) 3103 2231 27.6% 0.52 [0.40, 0.66] Total events 1103 1150 Heterogeneity: Tau2 = 0.03; Chi2 = 7.71, df = 2 (P = .02); I2 = 74% Test for overall effect: Z = 5.30 (P < .00001) 1.1.3 Aspirin Baron 2003 721 171 363 9.0% 0.80 [0.62, 1.03] 2003 Sandler 2003 43 259 70 258 7.1% 0.53 [0.35, 0.82] 2003 Logan 2008 99 434 121 419 8.4% 0.73 [0.53, 0.99] 2008 Benamouzig 2012 42 102 5.5% 1.06 [0.59, 1.91] 2012 33 83 Ishikawa 2014 73 0.69 [0.44, 1.08] 2014 152 159 6.8% Subtotal (95% CI) 1668 1282 36.8% 0.74 [0.63, 0.87] Total events 540 468 Heterogeneity: Tau2 = 0.00; Chi2 = 4.13, df = 4 (P = .39); I2 = 3% Test for overall effect: Z = 3.65 (P = .0003) 1.1.4 Calcium Baron 2015 [Calcium] 345 762 362 761 9.5% 0.91 [0.75, 1.12] 33 459 24 454 5.9% 1.39 [0.81, 2.39] 1999 Baron 1999 Bonithron 2000 28 176 36 178 5.9% 0.75 [0.43, 1.29] 2000 Subtotal (95% CI) 0.95 [0.73, 1.23] 1397 1393 21.3% Heterogeneity:  $Tau^2 = 0.02$ ;  $Chi^2 = 2.75$ , df = 2 (P = .25);  $I^2 = 27\%$ Test for overall effect: Z = 0.39 (P = .70) 1.1.5 Vitamin D 438 1024 442 1035 Baron 2015 [VitD] 9.7% 1.00 [0.84, 1.19] Subtotal (95% CI) 1024 1035 9.7% 1.00 [0.84, 1.19] 438 442 Total events Heterogeneity: Not applicable Test for overall effect: Z = 0.03 (P = .98) 0.71 [0.58, 0.87] Total (95% CI) 7263 6003 100.0% Total events 2509 2514 Heterogeneity: Tau2 = 0.10; Chi2 = 70.76, df = 12 (P < .00001); I2 = 83% Test for overall effect; Z = 3.35 (P = .0008) Favours Treatment Favours Placebo Test for subgroup differences:  $Chi^2 = 24.50$ , df = 4 (P < .0001),  $I^2 = 83.7\%$ 

Odds Ratio

Odds Ratio

Treatment

Placebo

Chapelle N, Martel M, Toes-Zoutendijk E, et al Recent advances in clinical practice: colorectal cancer chemoprevention in the average-risk population Gut 2020;69:2244-2255.

| Medication         | CRC mortality  | CRC incidence  | Adenoma/SSL incidence   | Safety  |
|--------------------|--|--|---|---|
| Aspirin            | Pooled RCT data: 33% lower<br>mortality over 20 yrs  | Pooled RCT data: 24% lower incidence over 20 yrs                                   | Meta-analysis of RCTs: 17% lower adenoma recurrence in those with prior adenoma / RCT: 35% lower adenoma recurrence in those with prior CRC     | Meta-analysis of RCTs: 59% higher<br>risk of major GI bleeding, 34%<br>higher risk of intracranial bleeding |
| Non-aspirin NSAIDs | RCT: no effect on mortality in those with CRC  | Meta-analysis of observational studies: 26% lower incidence                        | RCTs: 34-45% lower adenoma recurrence in those with prior adenoma   | Substantial cardiovascular (COX-2 inhibitors) and GI bleeding (non-selective NSAIDs) risks                  |
| Metformin          | Meta-analysis of observational studies: 25% lower mortality in those with CRC and diabetes | Meta-analysis of observational studies: 27% lower incidence in those with diabetes | RCT: 40% lower adenoma recurrence in non-diabetics / Meta-analysis of observational studies: 20% lower adenoma incidence in those with diabetes | Relatively safe, but mild GI side effects are common  |
| Calcium            |  | Prospective cohort: 22% lower incidence  | RCTs: mixed results   | Relatively safe   |
| Vitamin D          |  | RCT (vit D + calcium): no effect / Observational studies: mixed results            | RCT: no effect on adenoma recurrence or SSL incidence   | Relatively safe   |
| Folic acid         |  | Meta-analysis of RCTs: no effect   | Meta-analysis of RCTs: no effect on adenoma recurrence  | Relatively safe   |
| Statins            | Observational studies: mixed results   | MA observational and RCT:<br>Mixed results   | Observational studies: mixed results  | Relatively safe   |

Liang PS, Shaukat A. CGH 2021;19:1327-36

## Best Practice Advice

| Agent      | Recommendation  |
|------------|---|
| ASA        | 1) younger than 70 years with a life expectancy of at least 10 years, 2) have a 10-year cardiovascular disease risk of at least 10% a, and 3) not at high risk for bleeding |
| Metformin  | Type 2 Diabetics  |
| NSAIDs     |   |
| Calcium    |   |
| Vitamin D  | ×   |
| Statins    | ×   |
| Folic acid | ×   |

## **Future Directions**

- Combination?
- Food fortification?

• Tailored to age. sex and risk?





cified with a minimum of 25 units of Vitamin B



