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Changing the Future of PBC

Moving Towards Solutions

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Disclosures

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PBC Foundation

- 18,000 patients
- 90 countries, including 25 of 27 in EU
- Co-authors in guidelines, journal pieces, abstracts
- PREMs and PROMs recorded in App
- PBC 40
- Project 90/90
- International PBC Summit

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First, Do No Harm

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PBC Guidelines

Clinical Practice Guidelines

CrossMark

EASL JOURNAL OF HEPATOLOGY

EASL Clinical Practice Guidelines: The diagnosis and management of patients with primary biliary cholangitis☆

European Association for the Study of the Liver*

HEPATOLOGY

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PRACTICE GUIDANCE

Primary Biliary Cholangitis: 2018 Practice Guidance from the American Association for the Study of Liver Diseases

Lindor, Keith D.*[1]; Bowlus, Christopher L.[2]; Boyer, James[3]; Levy, Cynthia[4]; Mayo, Marlyn[5]

Author Information

Hepatology 69(1):p 394-419, January 2019. | *DOI:* 10.1002/hep.30145

Metrics

Editorial › Hepatol Int. 2022 Feb;16(1):1-23. doi: 10.1007/s12072-021-10276-6. Epub 2022 Feb 4.

APASL clinical practice guidance: the diagnosis and management of patients with primary biliary cholangitis

Hong You [# 1], Xiong Ma [# 2], Cumali Efe [# 3], Guiqiang Wang [4], Sook-Hyang Jeong [5], Kazumichi Abe [6], Weijia Duan [1], Sha Chen [1], Yuanyuan Kong [7], Dong Zhang [8], Lai Wei [9], Fu-Sheng Wang [10], Han-Chieh Lin [11], Jin Mo Yang [12], Tawesak Tanwandee [13], Rino A Gani [14], Diana A Payawal [15], Barjesh C Sharma [16], Jinlin Hou [17], Osamu Yokosuka [18], A Kadir Dokmeci [19], Darrell Crawford [20], Jia-Horng Kao [21], Teerha Piratvisuth [22], Dong Jin Suh [23], Laurentius A Lesmana [24], Jose Sollano [25], George Lau [26], Shiv K Sarin [27], Masao Omata [28 29], Atsushi Tanaka [30], Jidong Jia [31]

Affiliations + expand

PMID: 35119627 PMCID: PMC8843914 DOI: 10.1007/s12072-021-10276-6

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All Patients are Equal

But some patients are more equal than others

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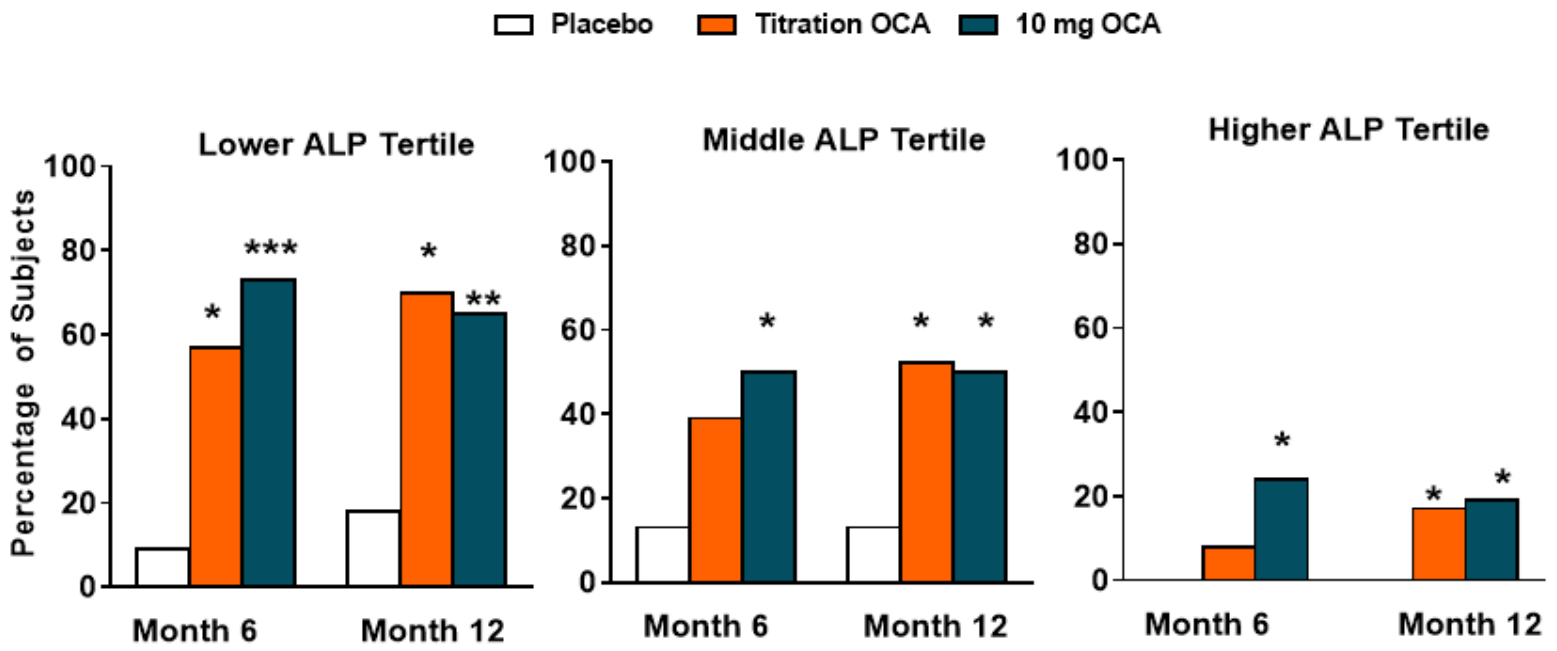
POISE

Percentage of Subjects Achieving Primary Composite Endpoint Summarized by Baseline ALP Tertile



Primary Endpoint at Month 12: Proportion of subjects achieving ALP <1.67x ULN with bilirubin ≤ULN and ≥15% reduction in ALP

Lower ALP Tertile, Baseline ALP <250.4 U/L; (Placebo n=22, Titration OCA n=23, OCA 10 mg n=26); **Middle ALP Tertile**, Baseline ALP ≥250.4 U/L to <341.9 U/L; (Placebo n=24, Titration OCA n=23, OCA 10 mg n=26); **Higher ALP Tertile**, Baseline ALP ≥341.9 U/L; (Placebo n=27, Titration OCA n=24, OCA 10 mg n=21).

*p<0.05, **p<0.01, ***p<0.0001; P values for comparing treatments were obtained using CMH General Association test stratified by randomization strata factor.

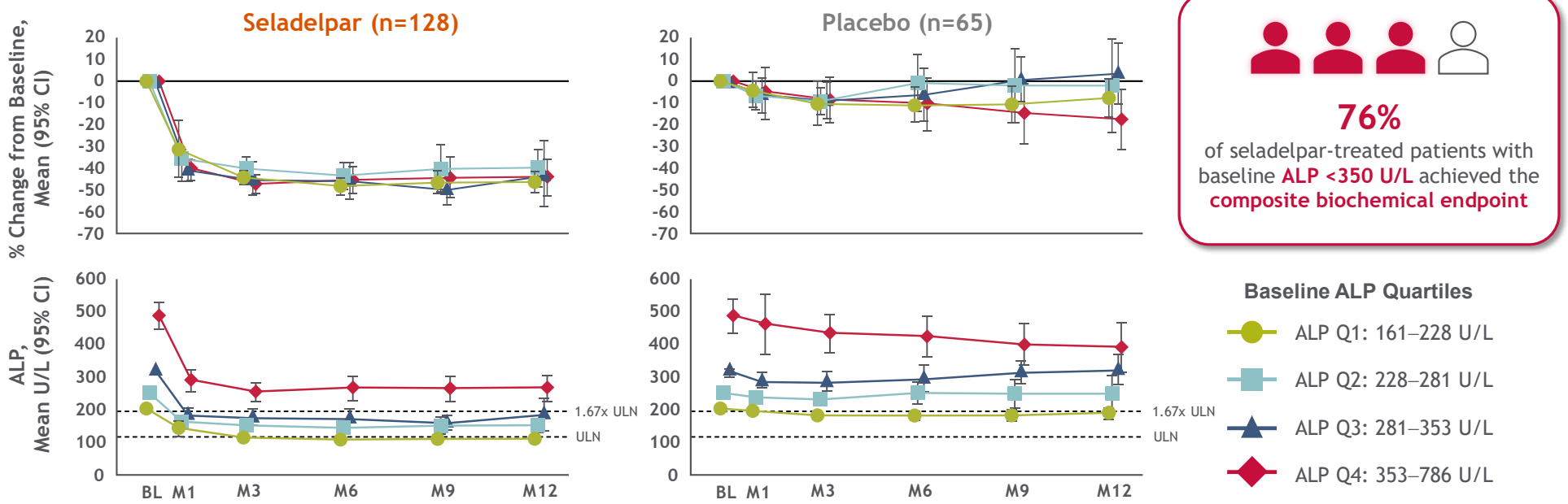
roup: 5 mg OCA for 6 months then titrated to 10 mg OCA if tolerated & ALP ≥1.67x ULN or bilirubin >ULN.

ndreone P, et al. Presented at AASLD 2014, The Liver Meeting, Boston. Poster 318.

ALP Changes by Baseline ALP Quartile

Analysis of seladelpar 10 mg vs placebo across baseline ALP quartiles up to Month 12 in the RESPONSE trial

ALP Changes by Baseline ALP Quartile



76%
of seladelpar-treated patients with baseline **ALP <350 U/L** achieved the **composite biochemical endpoint**

Seladelpar led to robust and consistent ALP improvement, regardless of baseline ALP

1 ALP ULN=116 U/L
ALP, alkaline phosphatase; BL, baseline; CI, confidence interval; M, month; PBC, primary biliary cholangitis; ULN, upper limit of normal; Q, quartile.
Kowdley K, et al. AASLD 2024. Poster #4339

It’s Just Patients

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Which Patients Might Benefit From ALP Normalization?

PARIS II response criteria
- ALP and AST < 1.5 × ULN and Normal TB

International cohort study

1047 patients with PBC
Adequate PARIS II response after ≥ 12 mo of UDCA

Normal ALP **(66%)** vs ALP 1-1.5 × ULN **(34%)**

Gain in 10-y survival in case of normal ALP levels?

Overall
in 1047 patients

7.6 mo
(95% CI: 2.7, 12.6)
P = .003

Subgroup analyses based on **age** and **liver stiffness**

Age > 62 y
AND
LSM < 10 kPa

1.8 mo
(95% CI: −5.0, 8.7)
P = .603

Age ≤ 62 y
OR
LSM ≥ 10 kPa

8.9 mo
(95% CI: 1.9, 15.9)
P = .013

Age ≤ 62 y
AND
LSM ≥ 10 kPa

52.8 mo
(95% CI: 45.7, 59.9)
P < .001

- LSM, liver stiffness measurement.
- Corpechot C, et al. Hepatology. 2024;79:39-48.

Which Patients Might Benefit From ALP Normalization?

Normal ALP greatest prognostic benefit in

- **Young Age <62yr**
- **Advanced Fibrosis LSM>10**

International cohort study

1047 patients with PBC
Adequate PARIS II response after ≥ 12 mo of UDCA

Normal ALP **(66%)** vs ALP 1-1.5 × ULN **(34%)**

Gain in 10-y survival in case of normal ALP levels?

Subgroup analyses based on **age** and **liver stiffness**

Overall in 1047 patients	Age > 62 y **AND** LSM < 10 kPa	Age ≤ 62 y **OR** LSM ≥ 10 kPa	Age ≤ 62 y **AND** LSM ≥ 10 kPa
7.6 mo (95% CI: 2.7, 12.6) *P* = .003	**1.8 mo** (95% CI: −5.0, 8.7) *P* = .603	**8.9 mo** (95% CI: 1.9, 15.9) *P* = .013	**52.8 mo** (95% CI: 45.7, 59.9) *P* < .001

- LSM, liver stiffness measurement.
- Corpechot C, et al. Hepatology. 2024;79:39-48.

Is It Really Just Patients?

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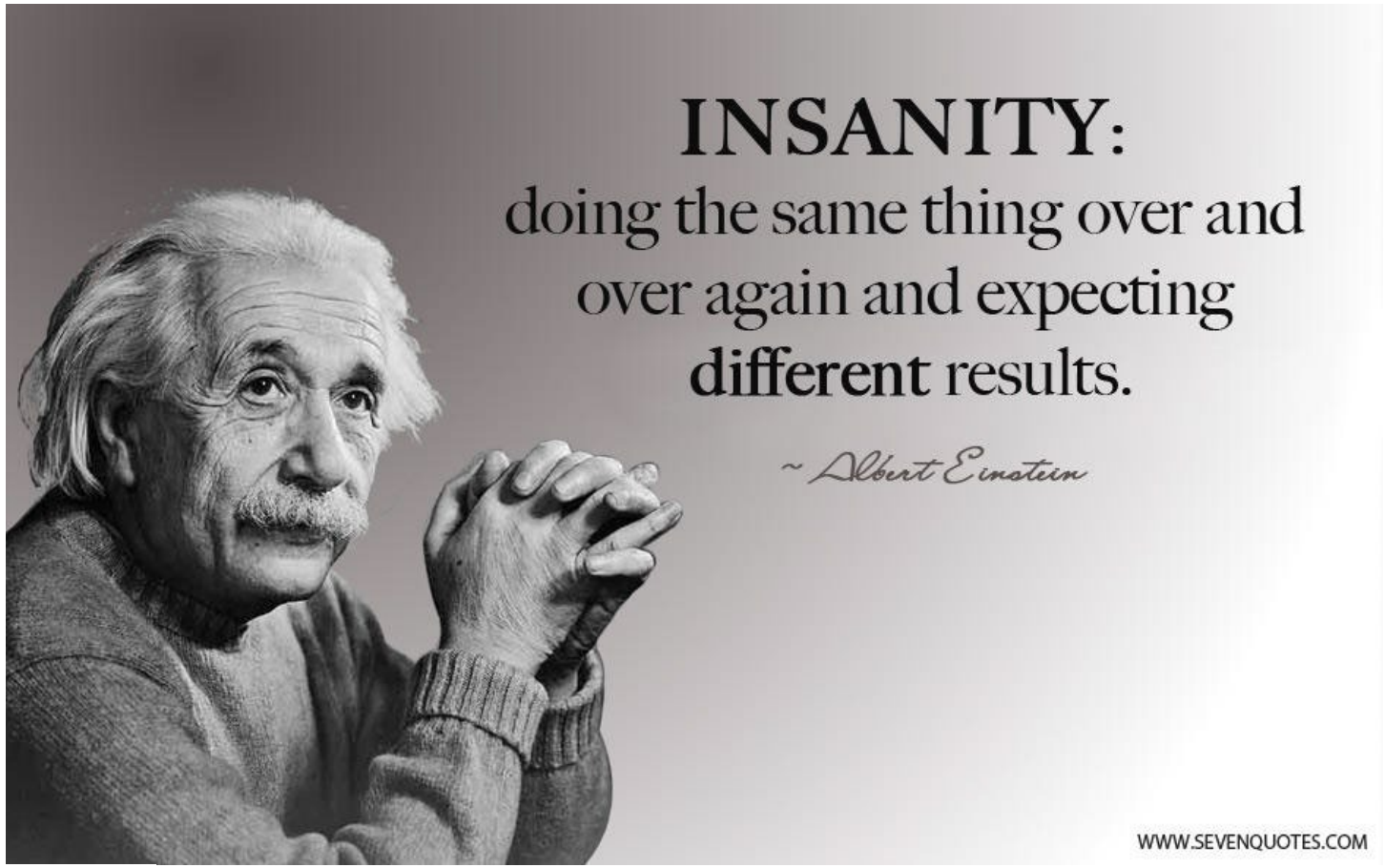
Are the Regulators Insane?!?



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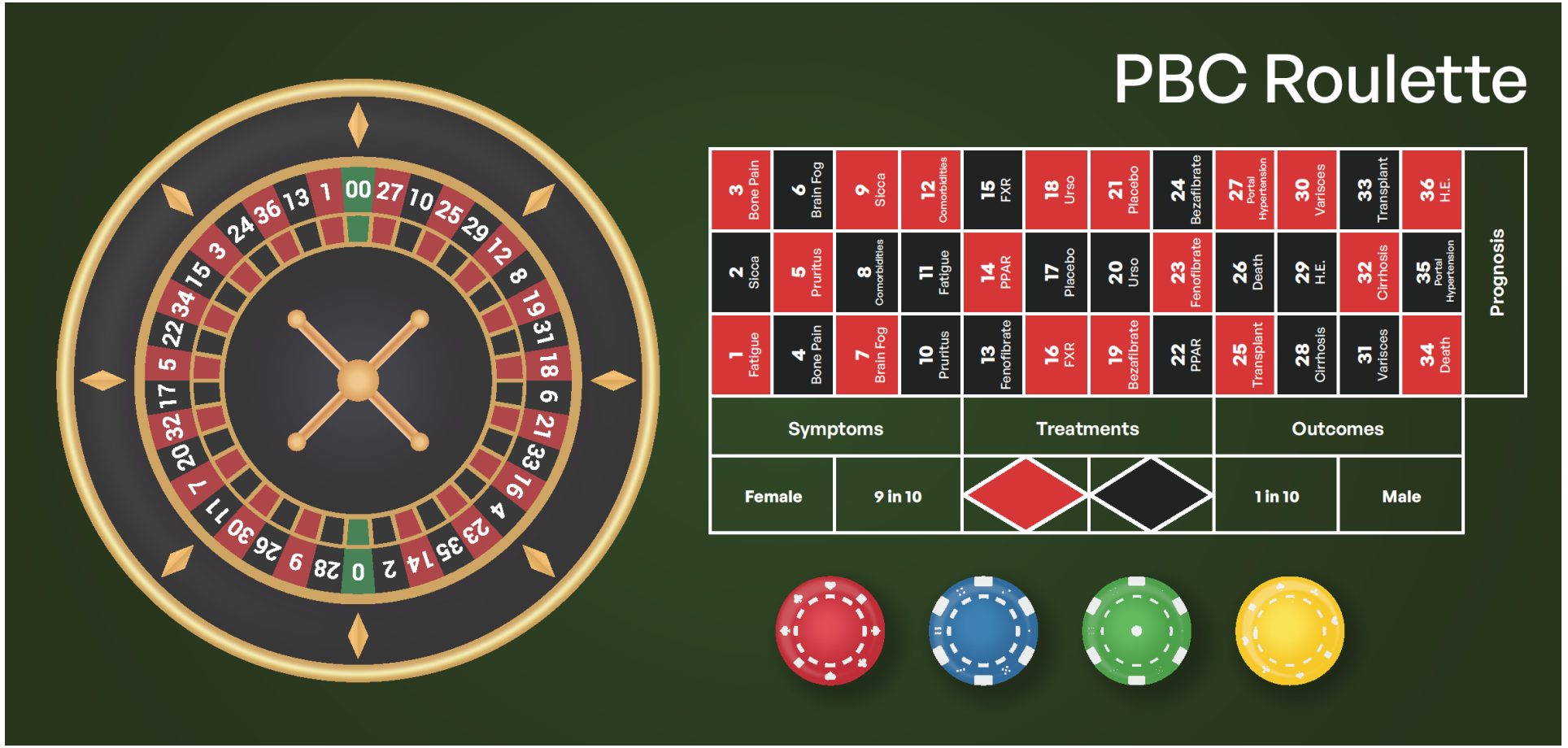
Gambling with Patients' Lives



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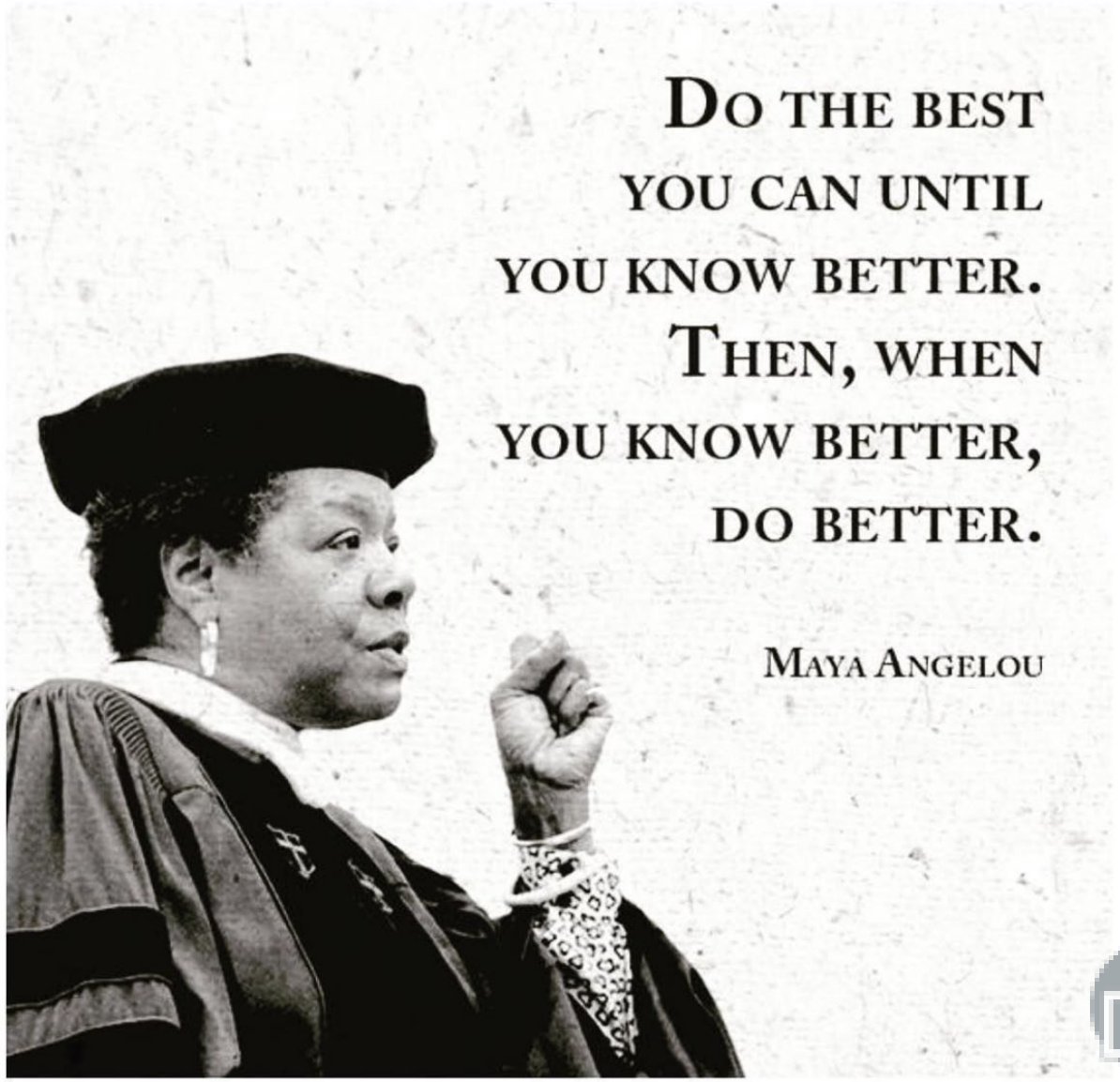
Moving Towards Solutions?

- Gold Standard
- RCTs are not random
- Unattainable ≠ negative
- Imperfections
- It’s OK to be wrong (and not even have to admit it)
- Be open to a better way

Moving Towards Solutions



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Thank you

If you think you are too small to make a difference, try sleeping with a mosquito in the room.

Dalai Lama

robert@pbcfoundation.international

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