

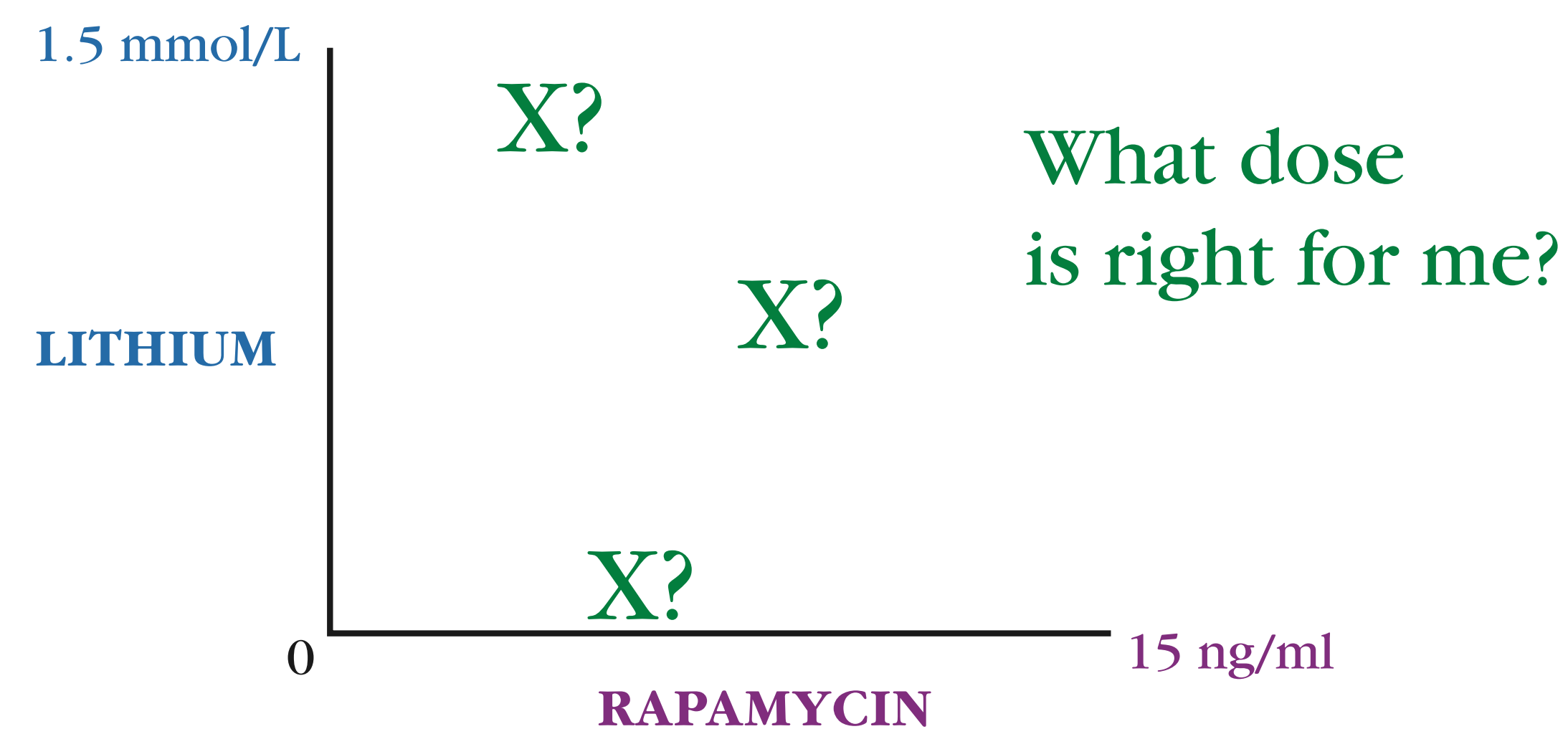
Tradeoffs between life extension and quality of life: A psychiatric perspective on practical pharmacological interventions

2022 American Aging Association Meeting

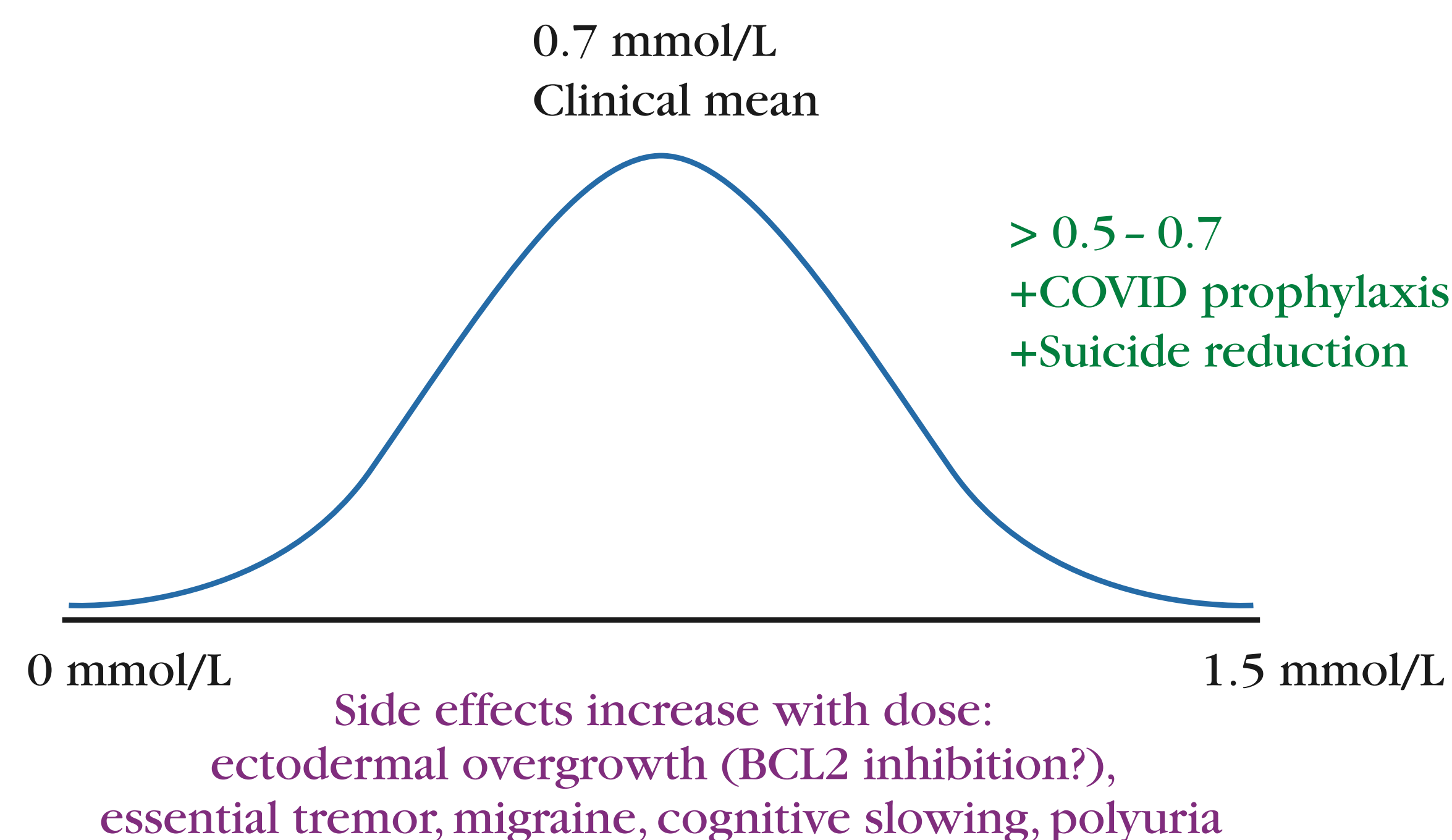
Jon Berner MD PhD • Woodinville Psychiatric Associates • jonbernermd@yahoo.com

Dose finding in the clinic: Moving from aggregate studies to single individuals

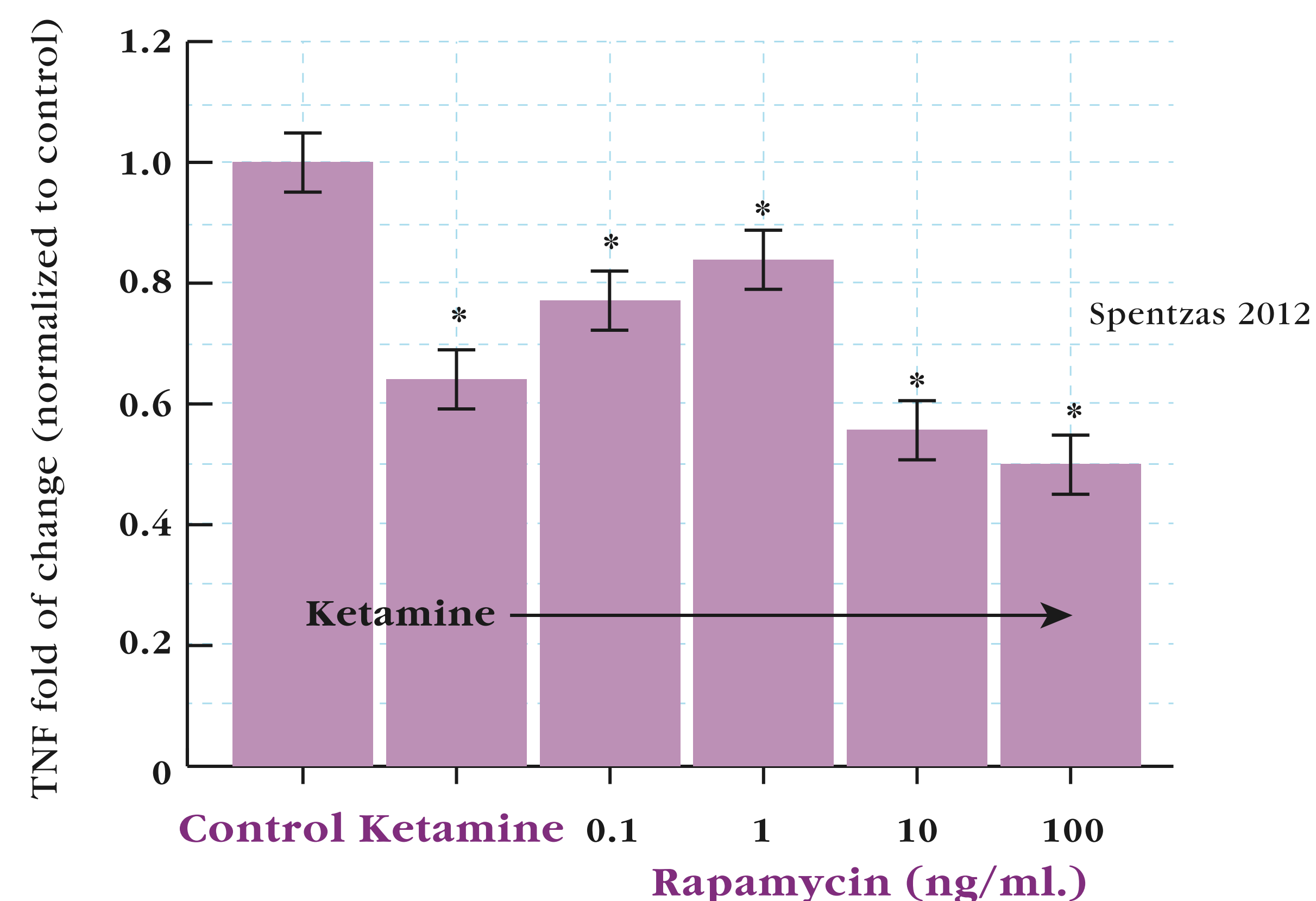
Can a human obtain the observed 30% increased longevity in *Drosophila*?



Optimal lithium dosing is non-linear: efficacy vs. tolerability tradeoffs



Optimal rapamycin dosing is non-linear: efficacy vs. tolerability tradeoffs Example: 4E-BP1 activity in vitro

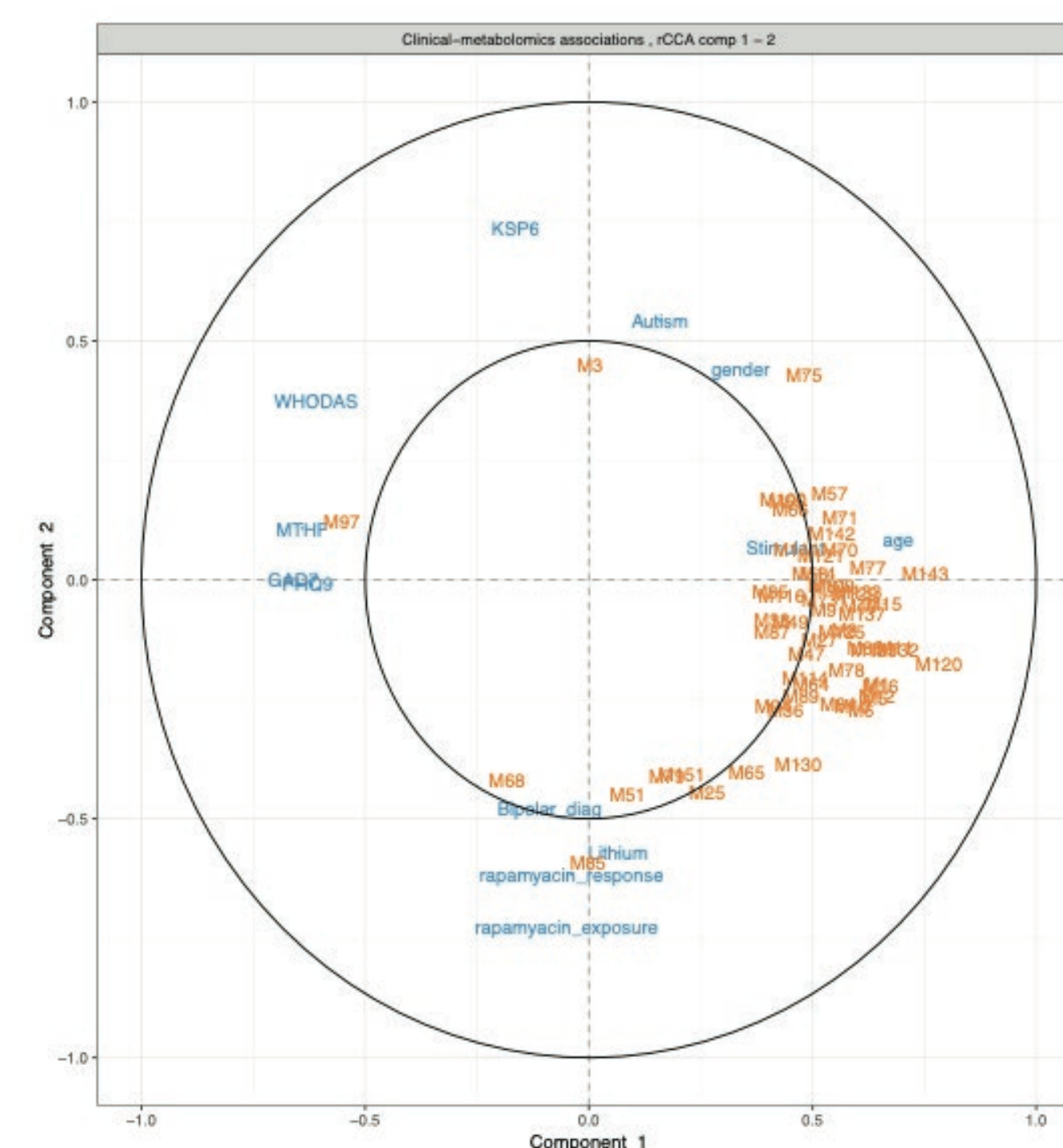


Even with ketamine, low dose rapamycin may increase inflammation from MRSA Prevalence rate 5-10% in a depressed and neurogenic pain population?

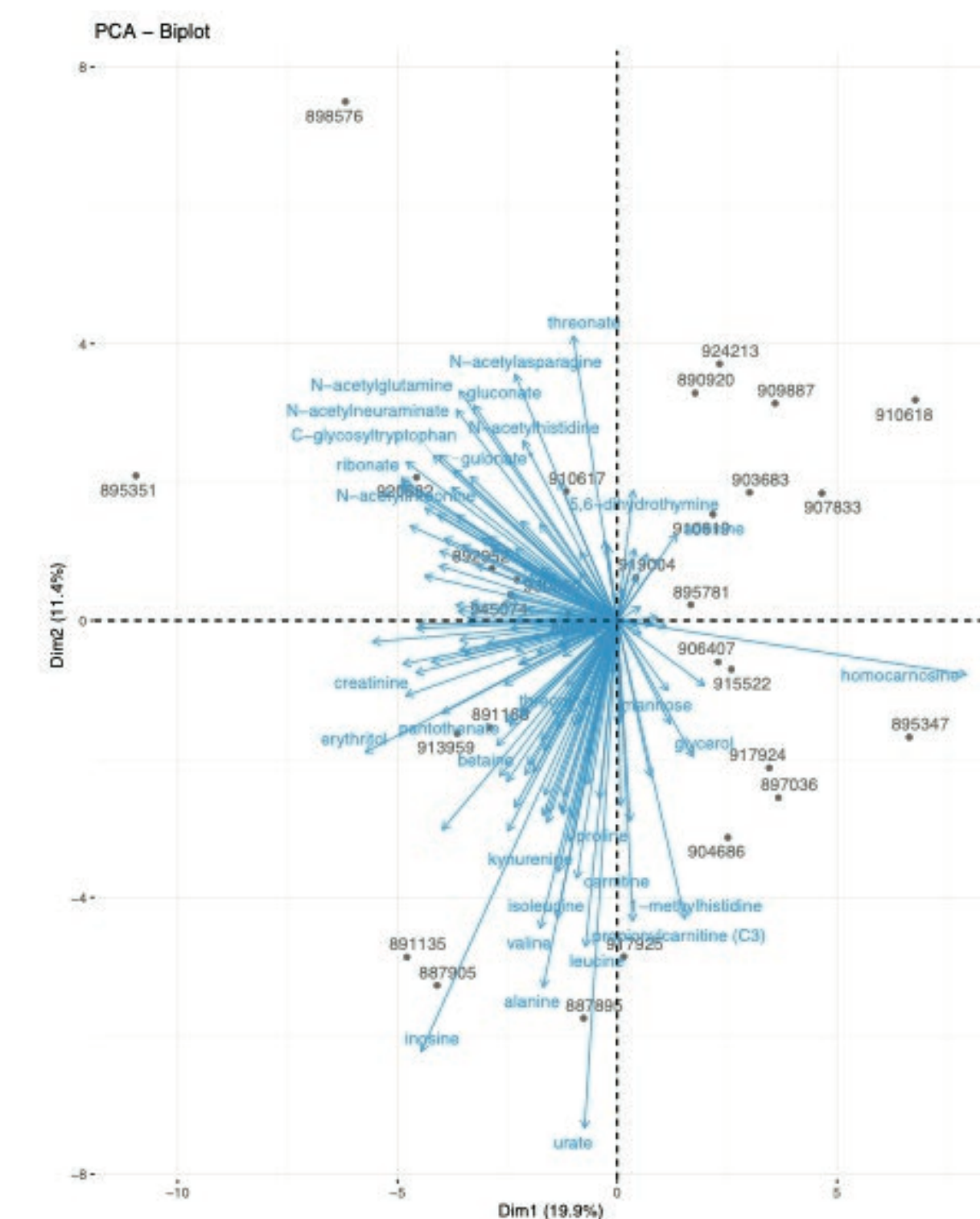
Cerebrospinal Fluid Maps: Are these useful navigational beacons?

• Patients, N=29, with depression refractory to current medications provided AM fasting CSF samples with subsequent z-score estimation of approximately 151 metabolites. Chart review provided subsequent response to medication treatment, contemporaneous clinical status with self-reported checklists, and basic demographic information. Hypothesis free multivariate analysis compressed the resultant 5000 item data array into 2 dimensions which collectively accounted for approximately 34% of the variance.

CSF analysis estimates the location of an individual in a finite population metabolomic space



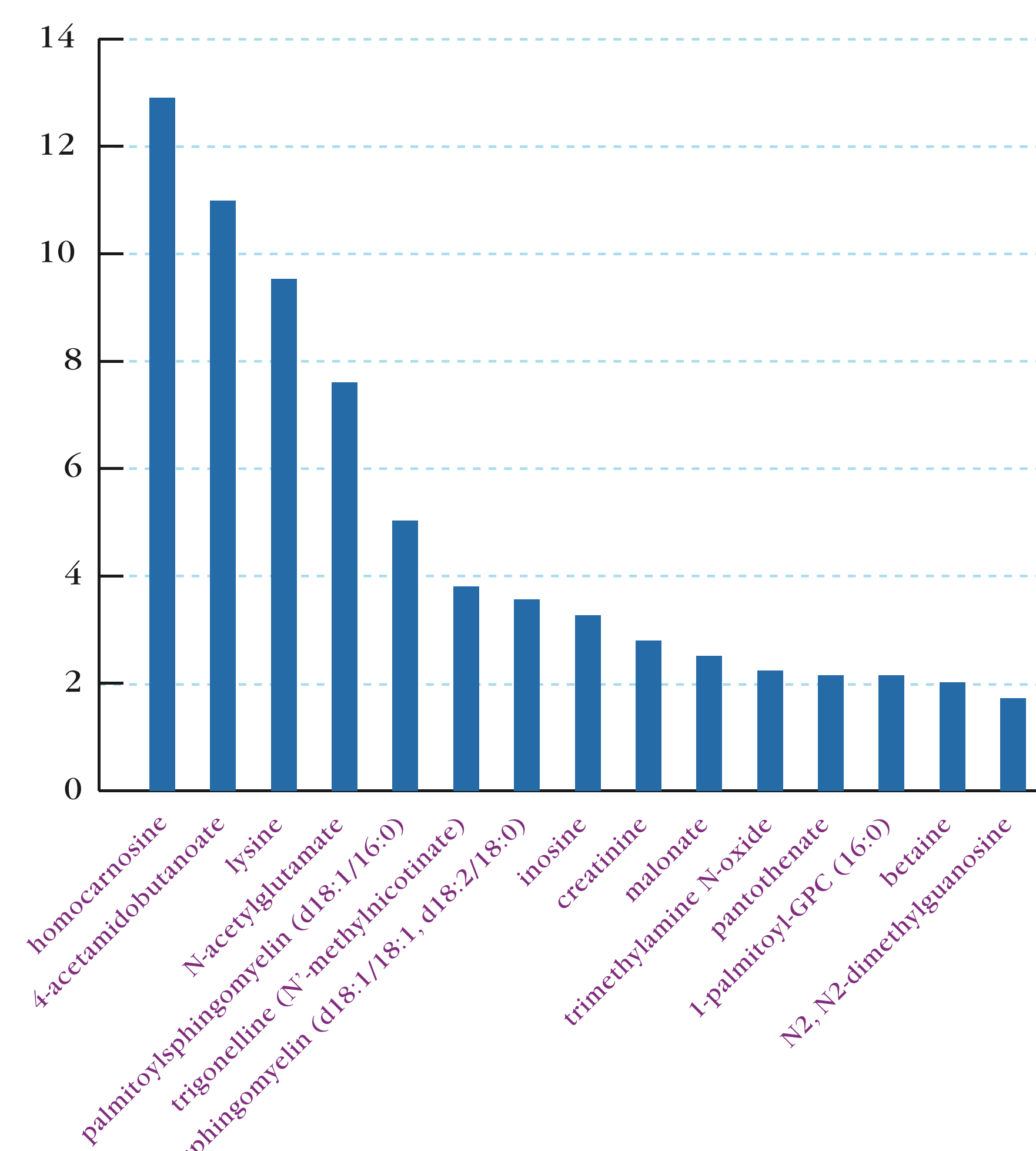
CSF mixed phenotypic and metabolic space



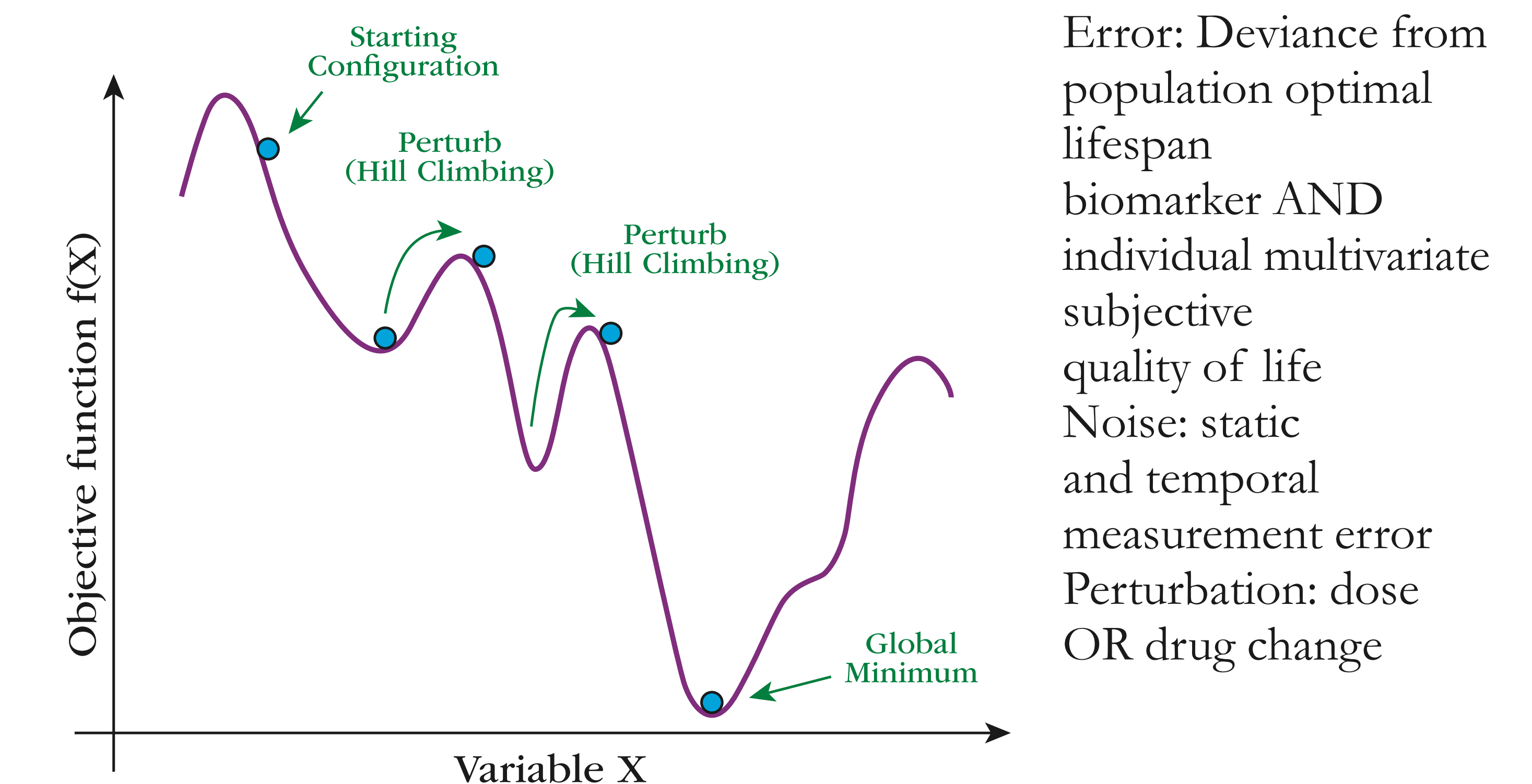
Age was regressed on the metabolites

A Random forest regression model was built using

- Metabolites (nr: 151) as predictors and
- Age as outcome variable
- 21.45% variation was explained by the metabolites
- Metabolites were ranked and top 15 metabolites were shown.



Optimizing results in a multivariate metabolic landscape with non-linear interactions Principles of gradient descent



LITHIUM Simulated annealing in practice: How clinicians manipulate the noise term

- Optimization is difficult. Optimal lithium dose finding in bipolar disorder often takes years. Premature gradient descent termination is the norm, not the exception. Treatment is usually “good enough” partial remission, rather than full remission. Frequent loss of efficacy, exit from a local minimum, to an unfavorable location, is the norm, not the exception, with polypharmacy changes OR age. Patient compliance is MUCH MORE important than the science.
- Measurement noise is poorly minimized systematically. In the chronic phases, dose step size is typically smaller and self-report error is often (not always) improved given temporal integration implied by less frequent visits.
- No objective linear markers of stability are available, e.g. fasting glucose in DM2

Subjective nearest neighbor prototype selection: Example of PPAR agonist selection

- Rationale: most clinical decision-making in community practice is driven by prototype matching rather than diagnostic checklists with hard thresholds. Clinical complexity ALWAYS exceeds working memory span: 7 +/- 2 items
- Most of the variance is not measured by CSF (> 65%) even with the assumption that CSF has a high correlation with underlying glial and neuronal metabolism
- Patient pattern matching between their own personal narrative and other individual narratives massively decreases the noise term in the optimization problem
- Clinical example: PPAR agonist for chronic fatigue.
- Scaling is trivial in the context of ongoing experienced physician supply constraints, e.g. metabolic Facebook