Guiding clinical trial design for a rare disease using natural history data and Bayesian disease progression modeling

Barbara Wendelberger

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Acknowledgements

- Berry Consultants
  - Melanie Quintana, Scott Berry
- National Human Genome Research Institute, National Institutes of Health
  - Julie Sapp, Leslie Biesecker

Pathogenetic insights from quantification of the cerebriform connective tissue nevus in Proteus syndrome

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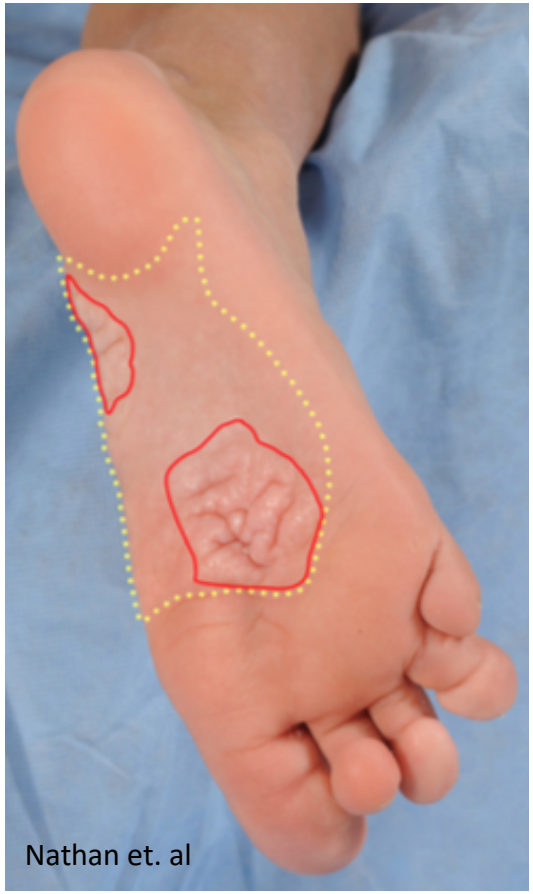
Bethesda, Maryland

Rare disease

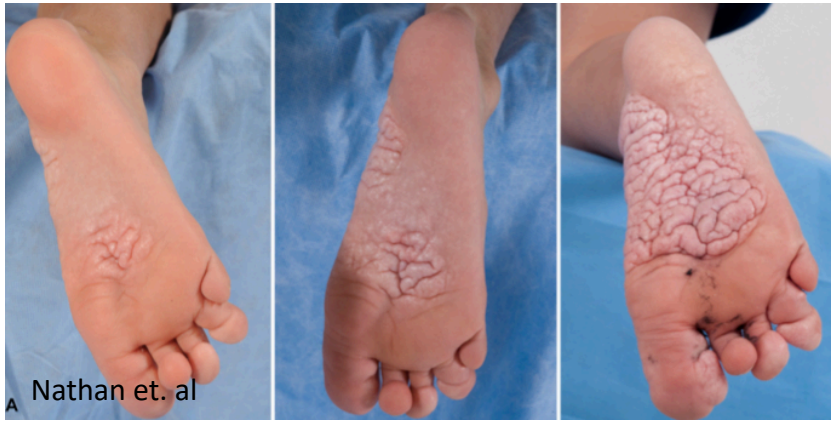
Proteus syndrome

- Disease characterization and manifestation
  - Genetic mutation
  - Overgrowth of skin, bone, and other tissues
  - Plantar cerebriform connective tissue nevus (CCTN)
- Challenges in clinical trial design
  - Small, heterogenous patient populations
  - Insufficient understanding of disease etiology
  - Poorly developed study endpoints


Nathan et. al

Natural history study

CCTN disease progression



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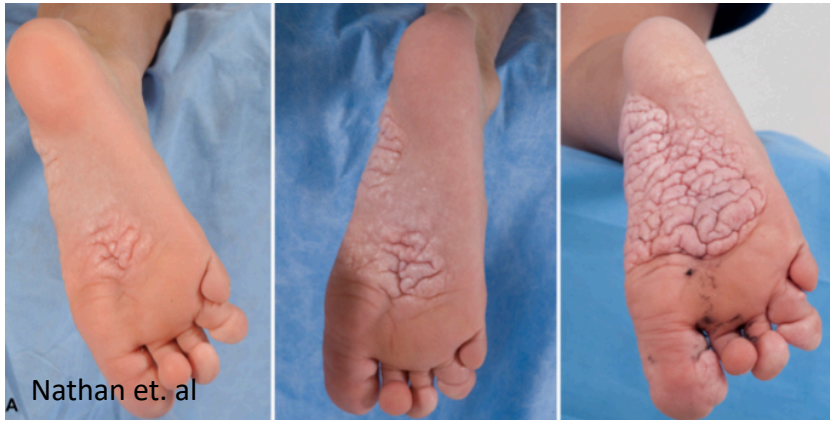

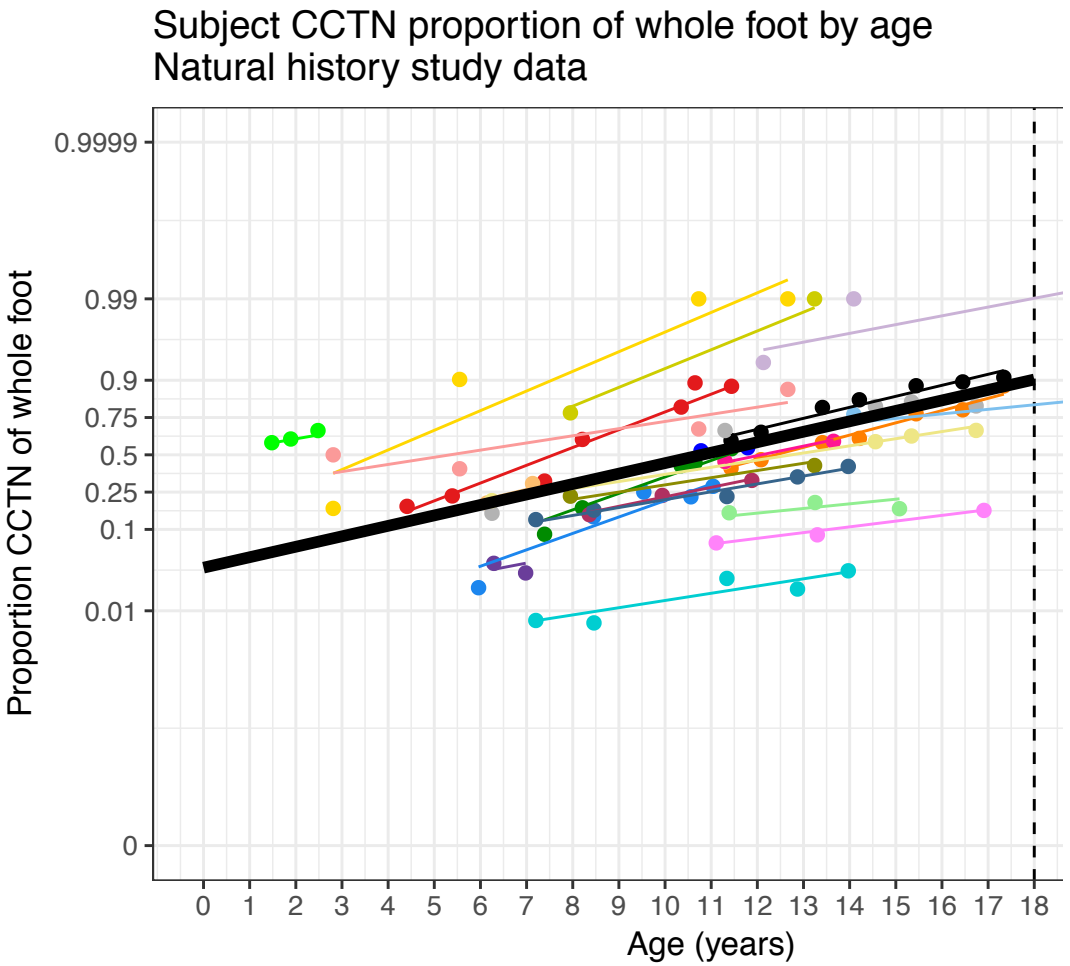

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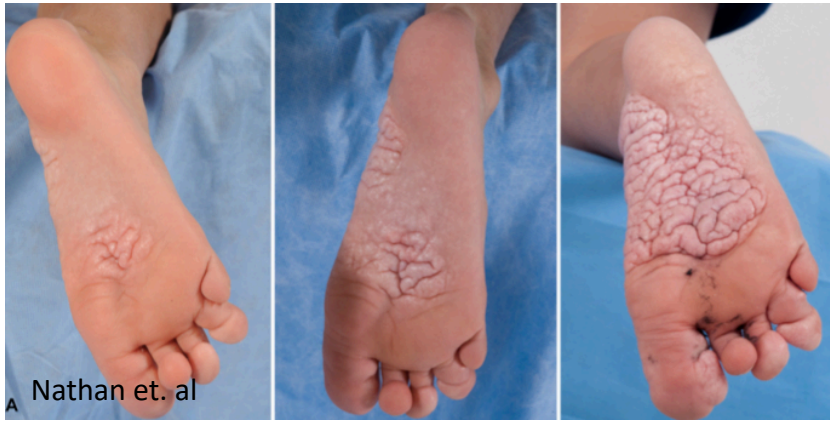

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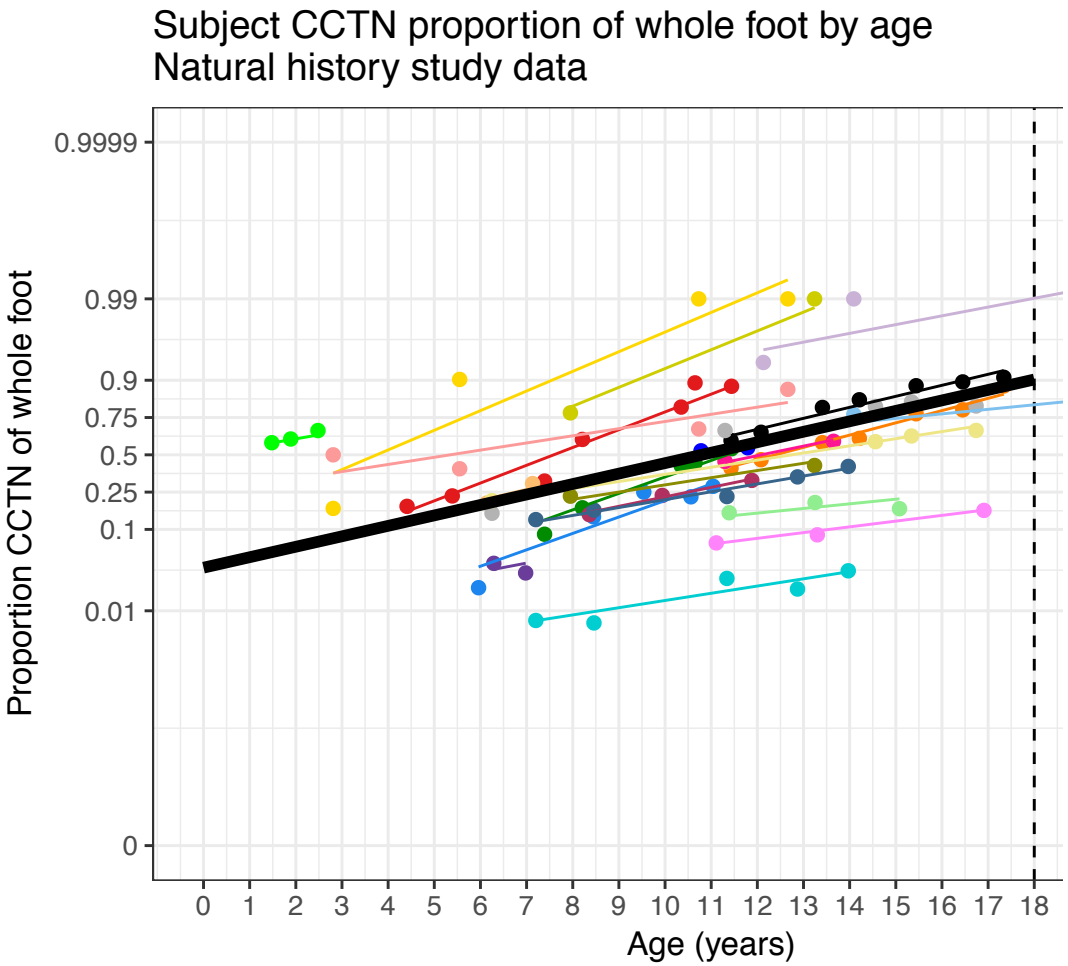

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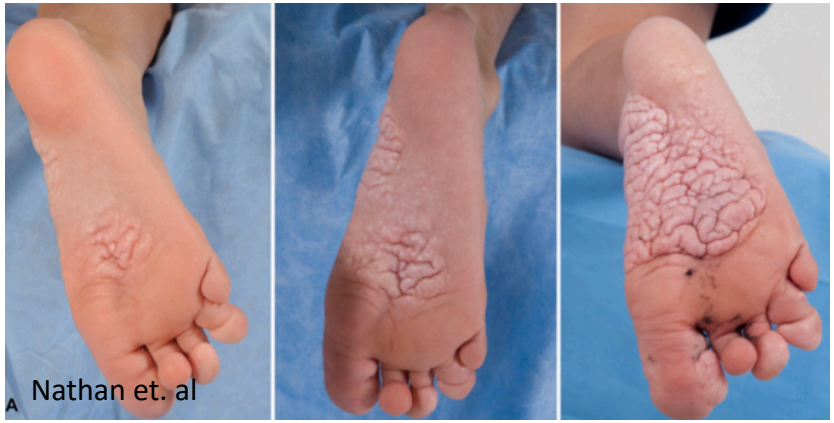

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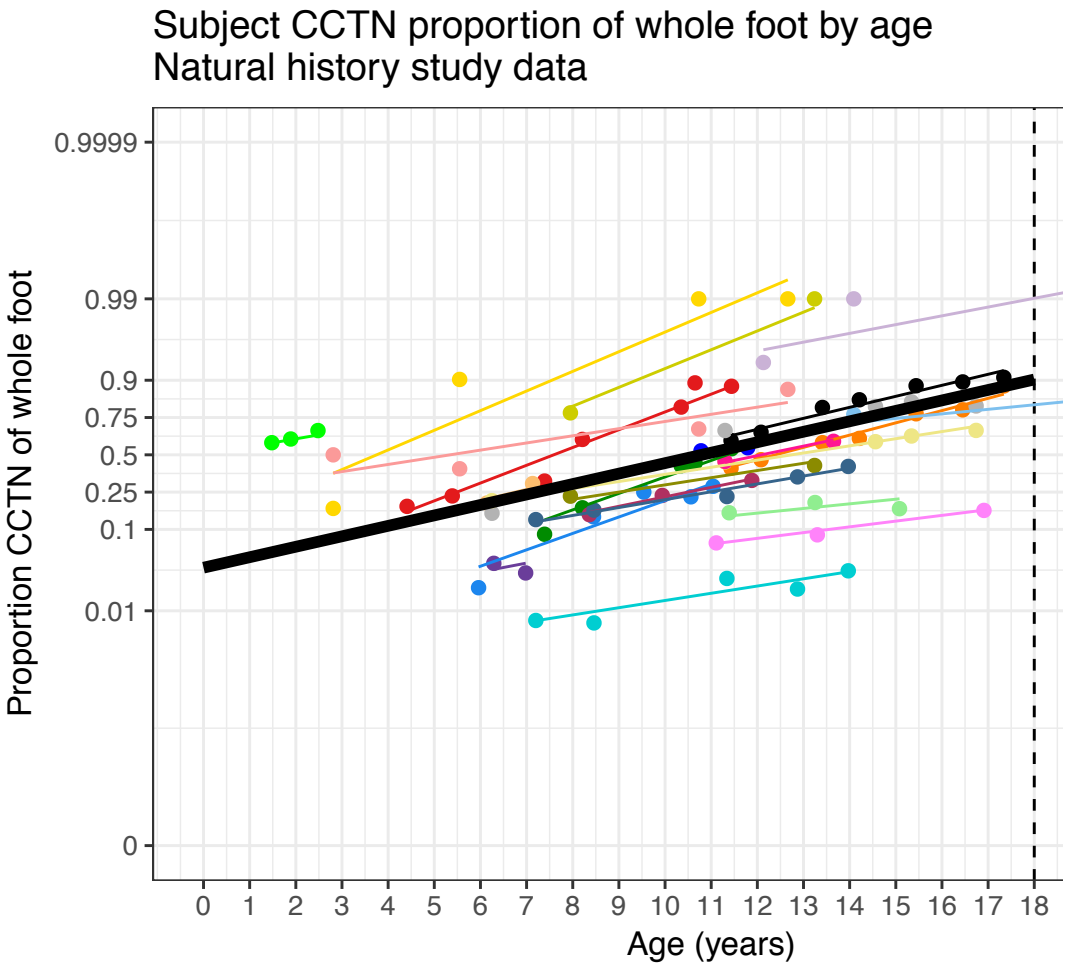

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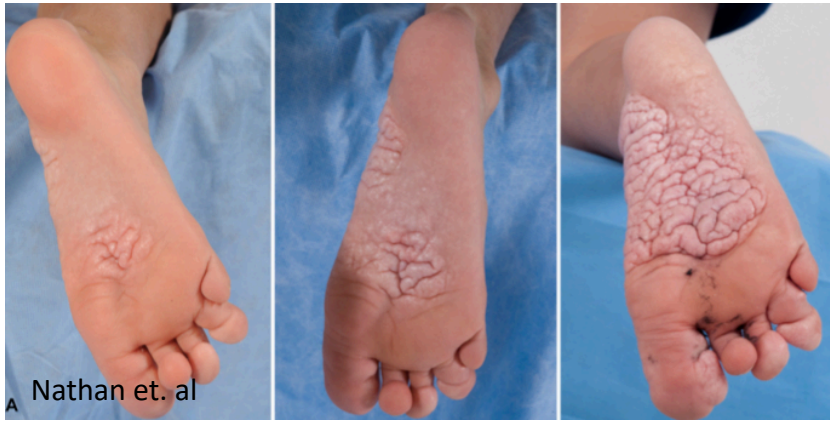

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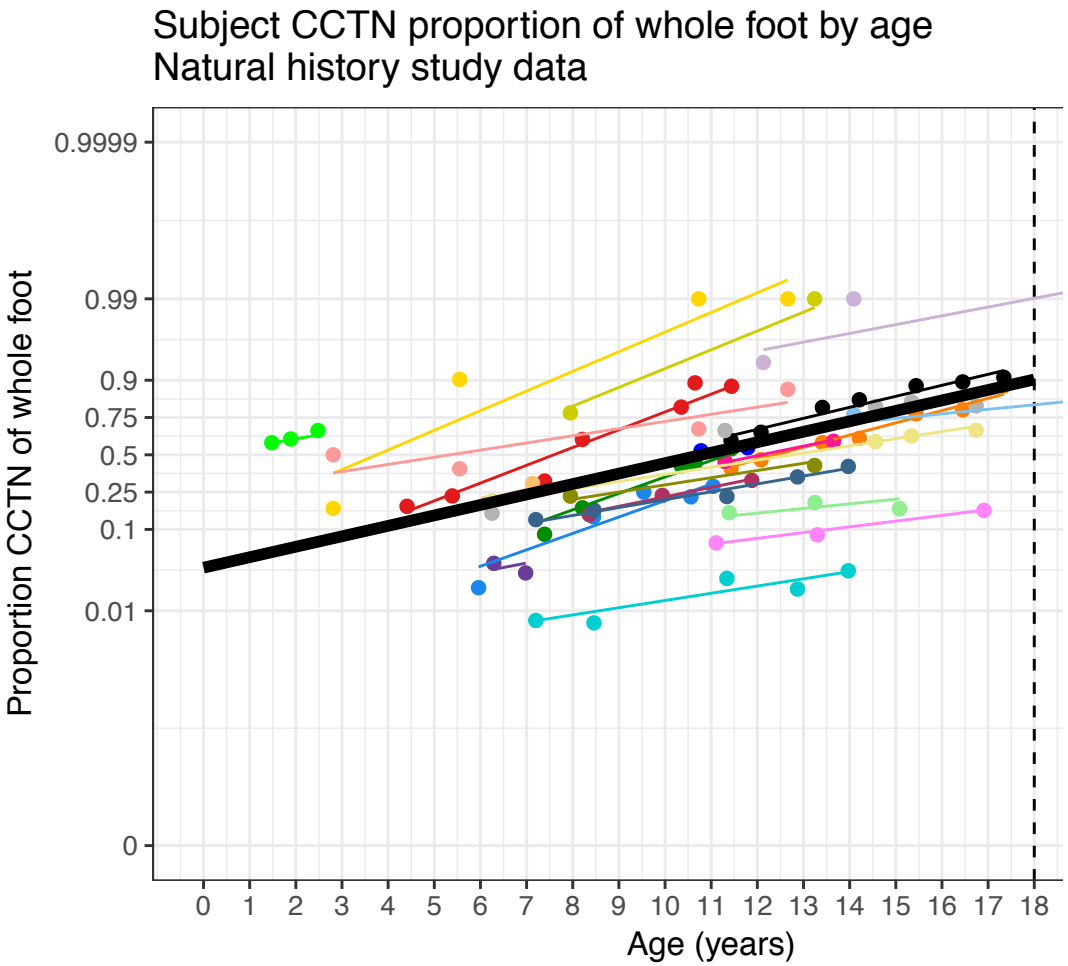
-create a virtual subject simulator
-simulate a treatment effect



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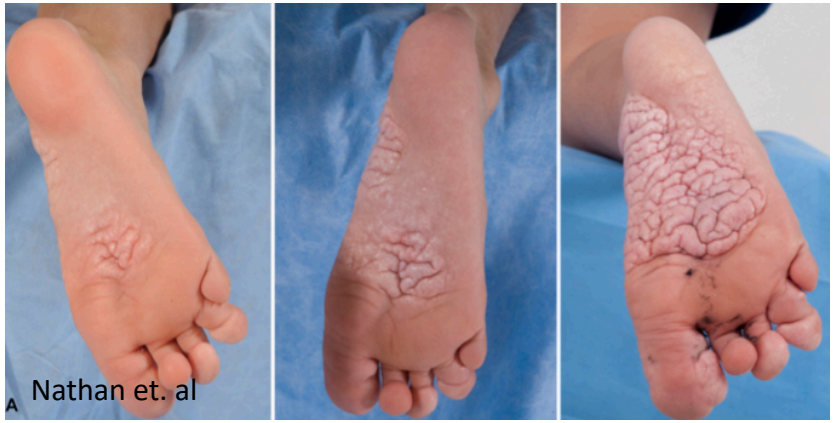

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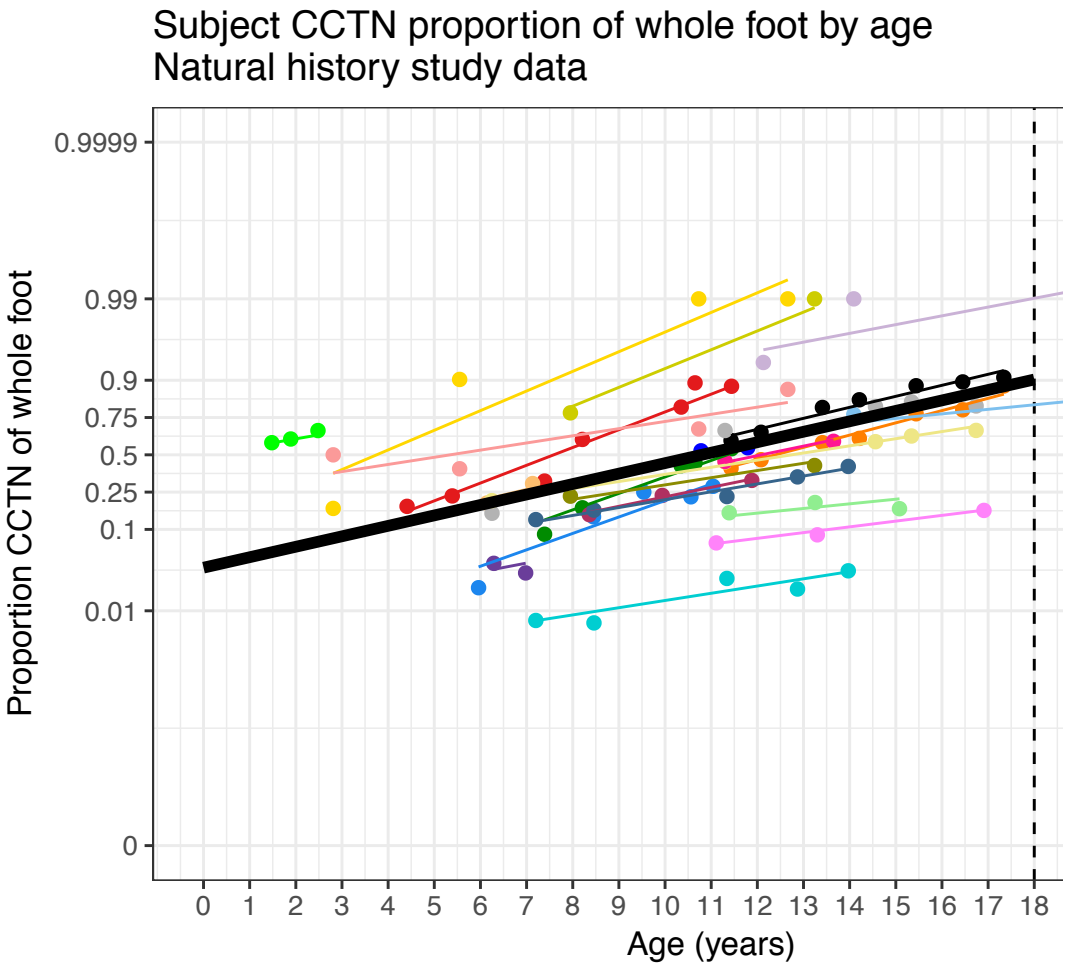

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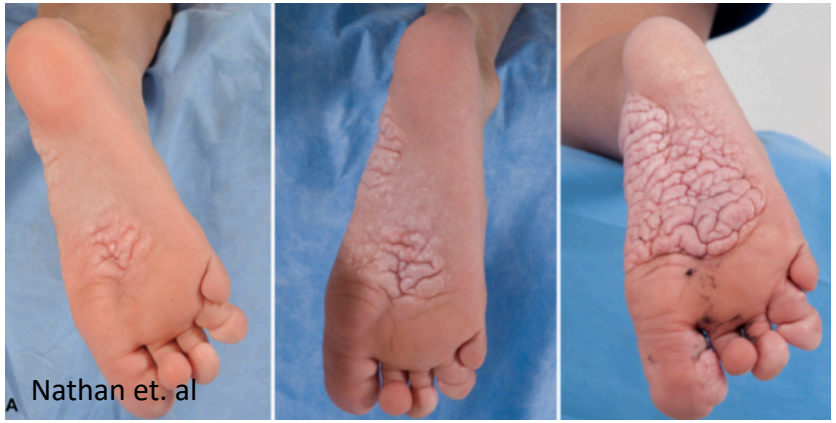

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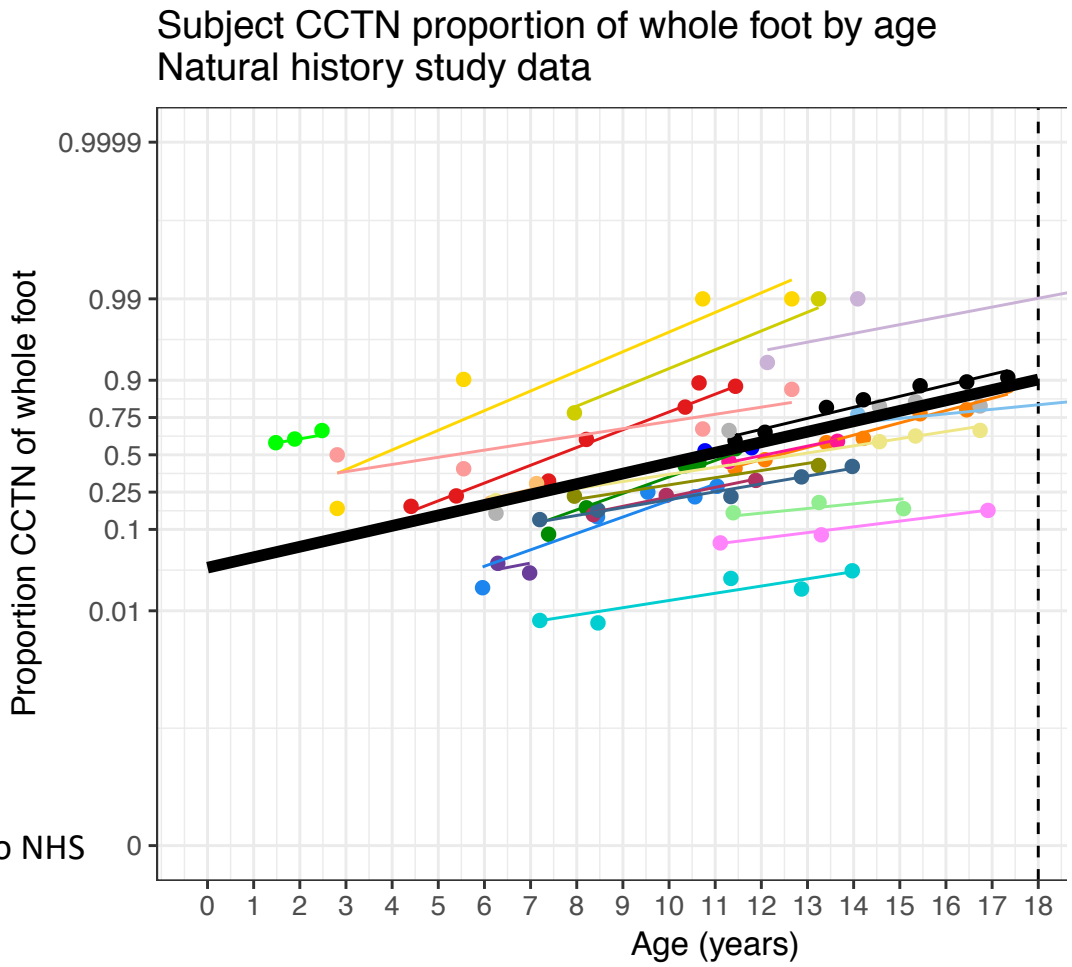
-design a single arm trial that
  - compares disease progression of treated patients to NHS
  - defines a final analysis using the DPM



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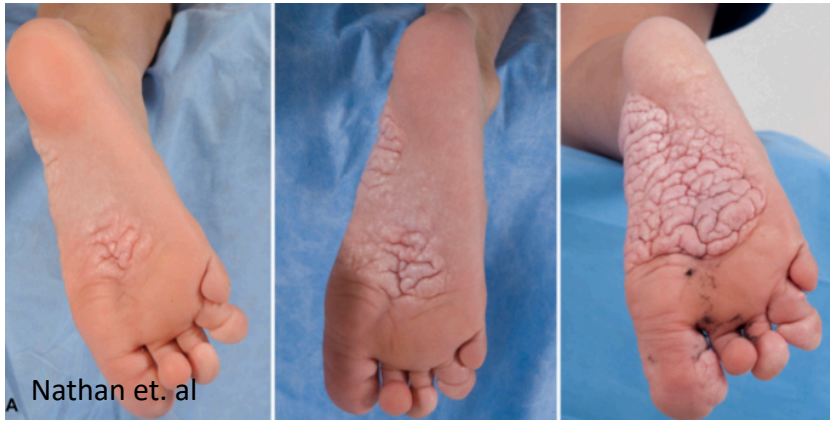

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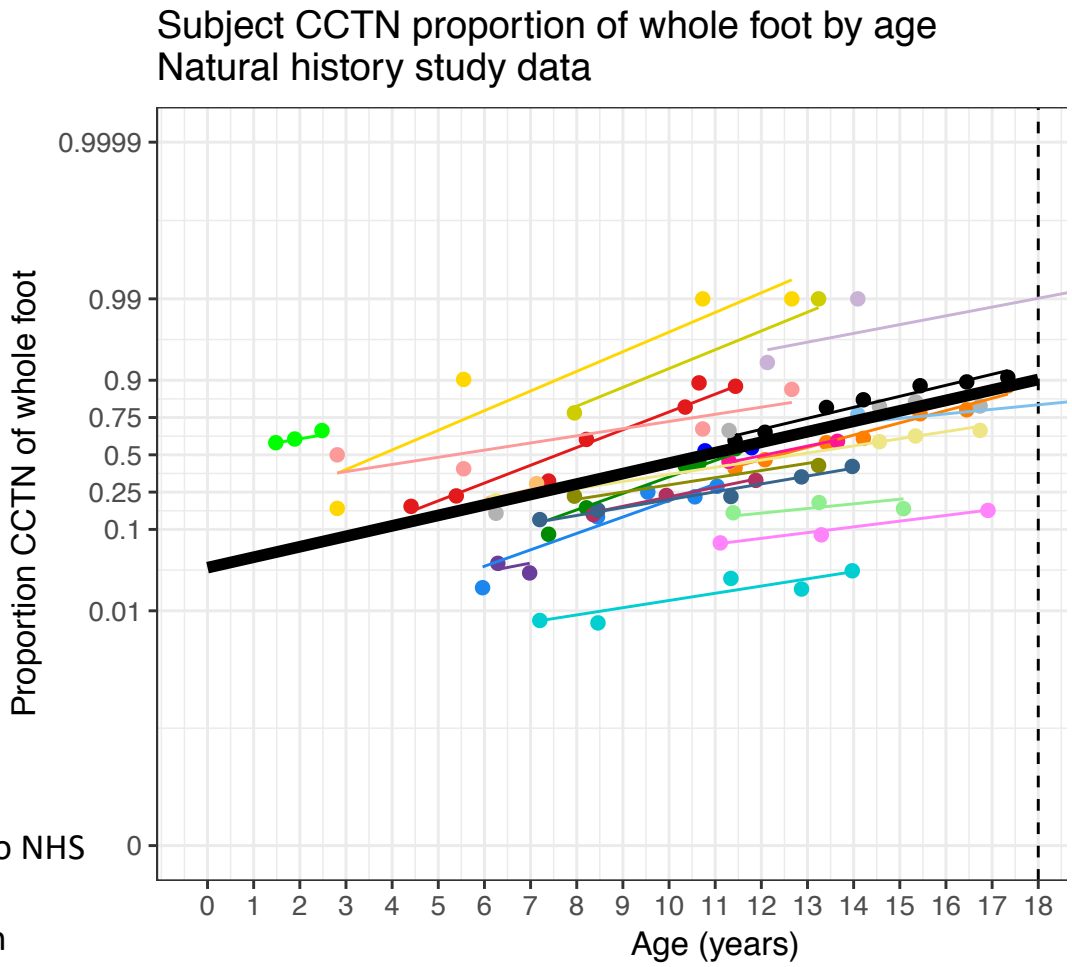
  - defines a final analysis using the DPM
-understand the operating characteristics of this design

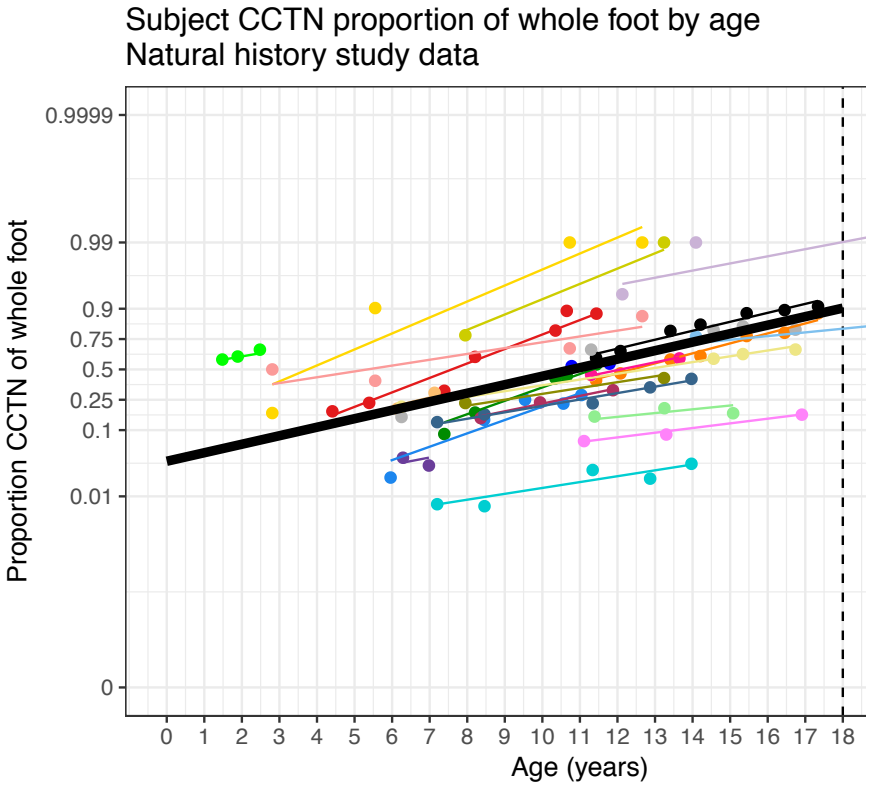


Natural history study

CCTN disease progression

Fit a mixed model to estimate random slope and intercept for age

For subject *s* at visit *i*: $logit(CCTN_{si}) = \beta_{0,s} + \beta_{1,s} * Age_{si} + \varepsilon_{si}$



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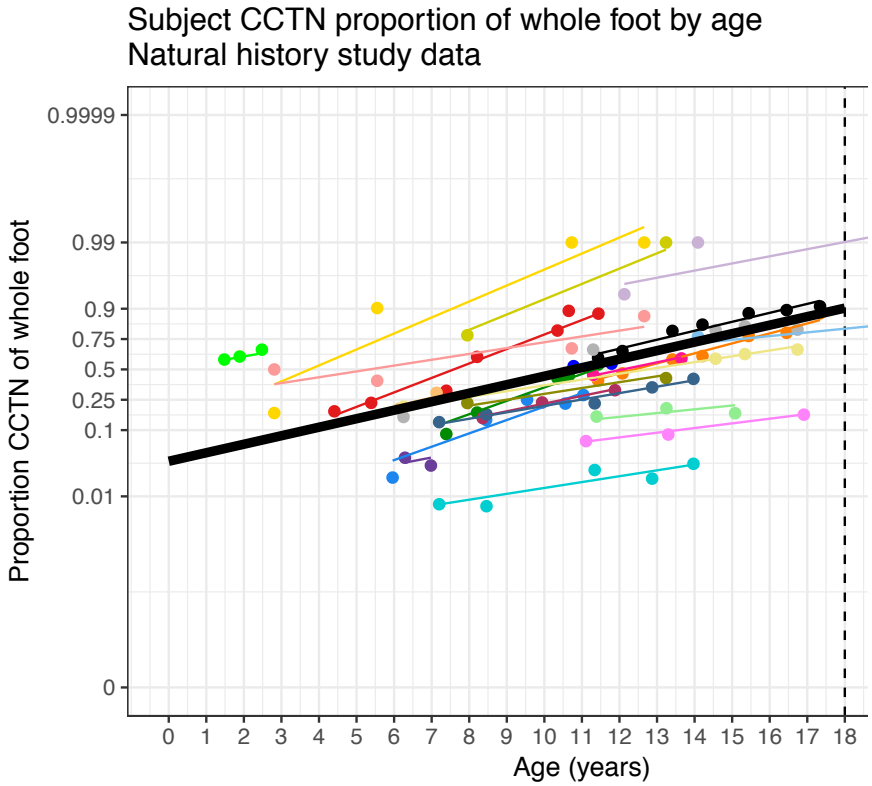

Estimates:

μ_{β_0}: mean random intercept

$\sigma^2_{\beta_0}$: variance random intercept

μ_{β_1}: mean random slope

$\sigma^2_{\beta_1}$: variance random slope

σ^2_{ε} : residual error

CCTN simulation model

Virtual patient simulator

Use mixed model estimates to simulate virtual patients

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Natural history of disease progression

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Natural history of disease progression

$$\beta_{0,s} \sim Normal(\mu_{\beta_0}, \sigma^2_{\beta_0})$$

$$\beta_{1,s} \sim Gamma(\frac{\mu^2_{\beta_1}}{\sigma^2_{\beta_1}}, \frac{\mu_{\beta_1}}{\sigma^2_{\beta_1}})$$

$$\varepsilon_{si} \sim Normal(0, \sigma^2_{\varepsilon})$$

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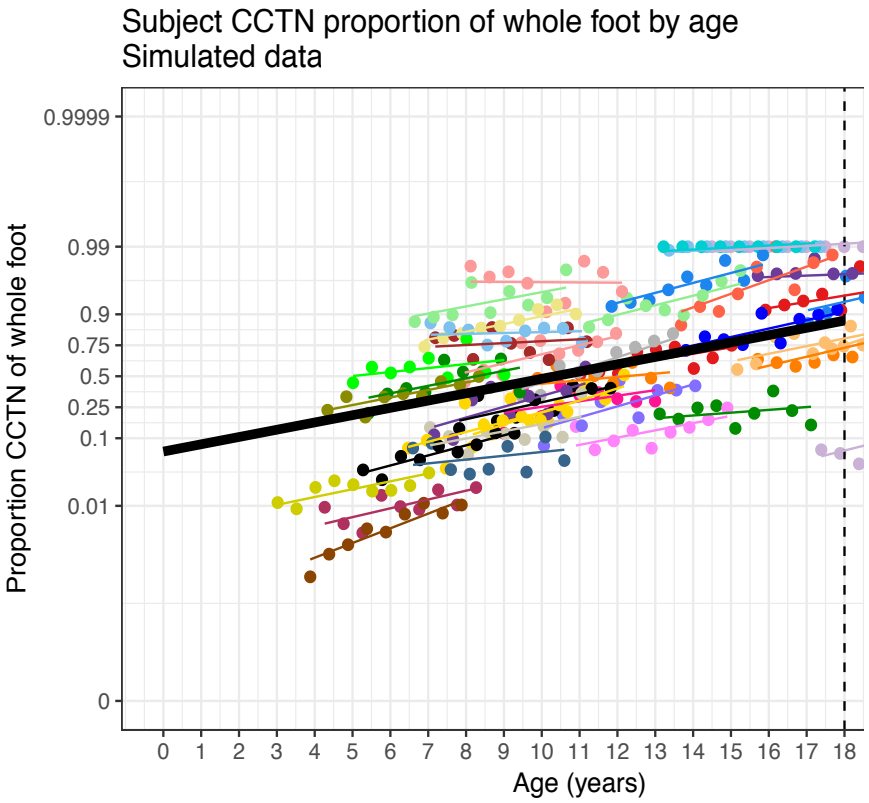

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$$\varepsilon_{si} \sim Normal(0, \sigma^2_{\varepsilon})$$

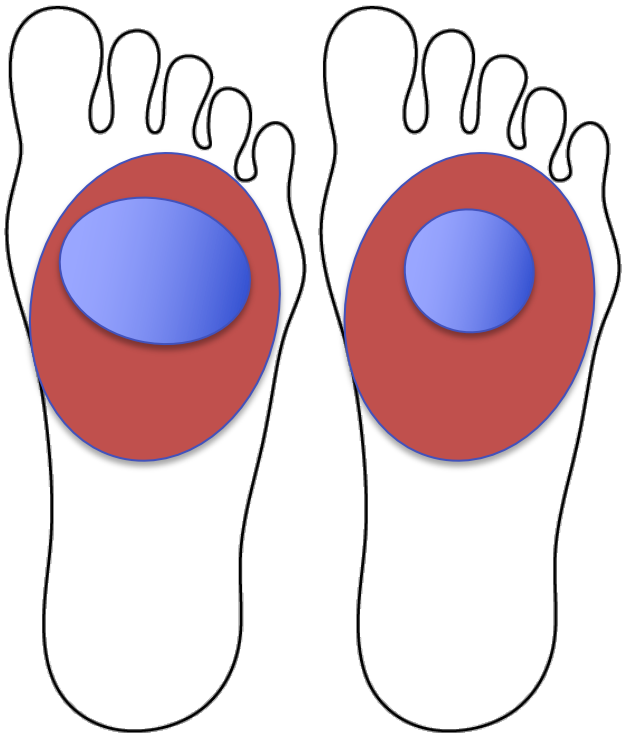
Use mixed model parameter estimates to create a virtual patient simulator that can generate patients with the same characteristics as the NHS patients

Assume that baseline age is distributed as a truncated normal.

Simulating a treatment effect

Proportional slowing of CCTN progression

- Treatment effect may *slow, stop,* or *reduce* disease progression of CCTN (measured as a proportion of the whole foot)
- Here, we are simulating CCTN and examining treatment effects applied to CCTN measurements



Simulating a treatment effect

Proportional slowing of CCTN progression

- Treatment effect, $\boldsymbol{\theta}$, is applied to the slope parameter of the simulation model
  - Only for the years during which the patient was treated

Years treated

$$logit(CCTN_{si}) = \boldsymbol{\beta}_{0,s} + (\boldsymbol{\beta}_{1,s} * Age_{s0}) + (\boldsymbol{\theta} * \boldsymbol{\beta}_{1,s} * (Age_{si} - Age_{s0})) + \boldsymbol{\varepsilon}_{si}$$

Natural history of disease progression

Treated disease progression

Simulating a treatment effect

Proportional slowing of CCTN progression

- Treatment effect, $\boldsymbol{\theta}$, is applied to the slope parameter of the simulation model
  - Only for the years during which the patient was treated
- The addition of $\boldsymbol{\theta}$ effectively models proportional slowing of CCTN progression

Years treated

$$logit(CCTN_{si}) = \boldsymbol{\beta}_{0,s} + (\boldsymbol{\beta}_{1,s} * Age_{s0}) + (\boldsymbol{\theta} * \boldsymbol{\beta}_{1,s} * (Age_{si} - Age_{s0})) + \boldsymbol{\varepsilon}_{si}$$

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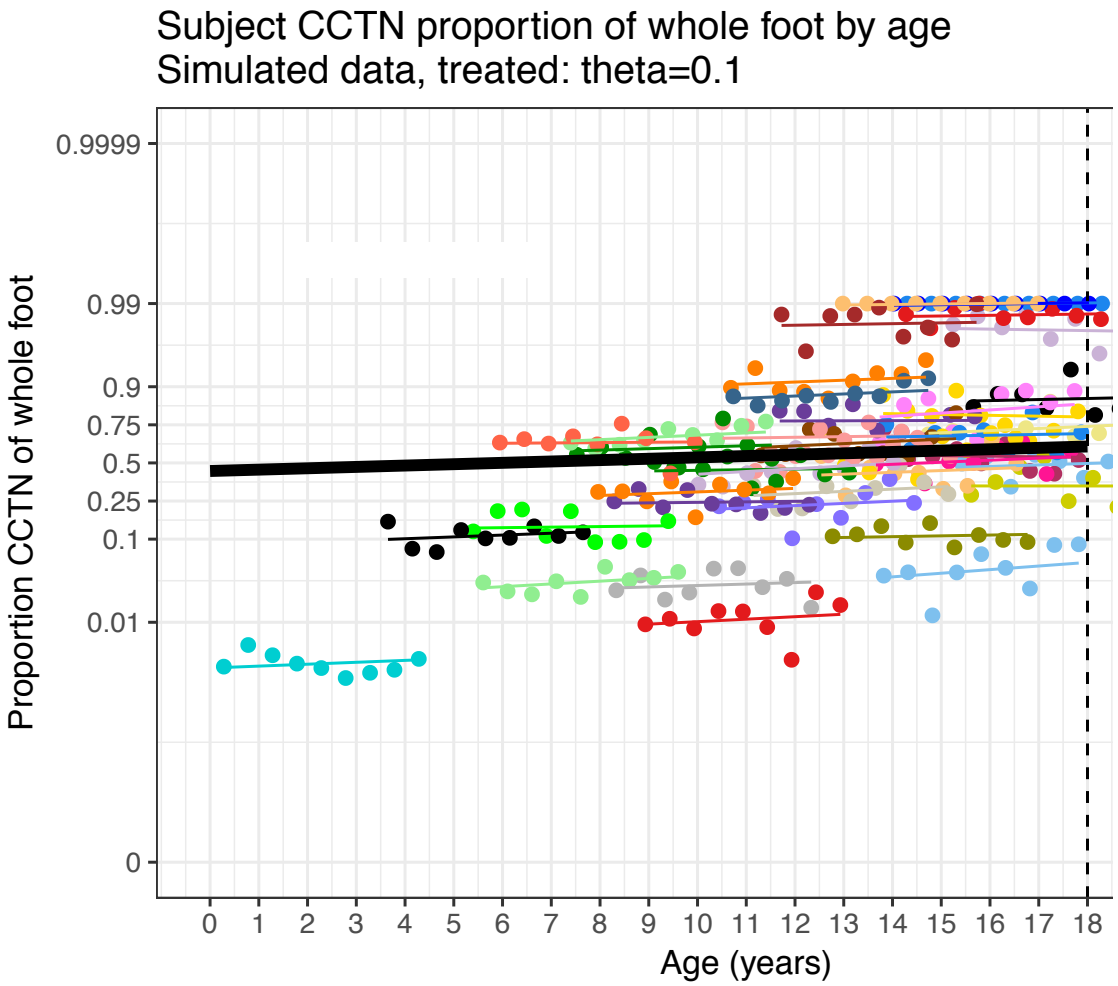

Simulating a treatment effect

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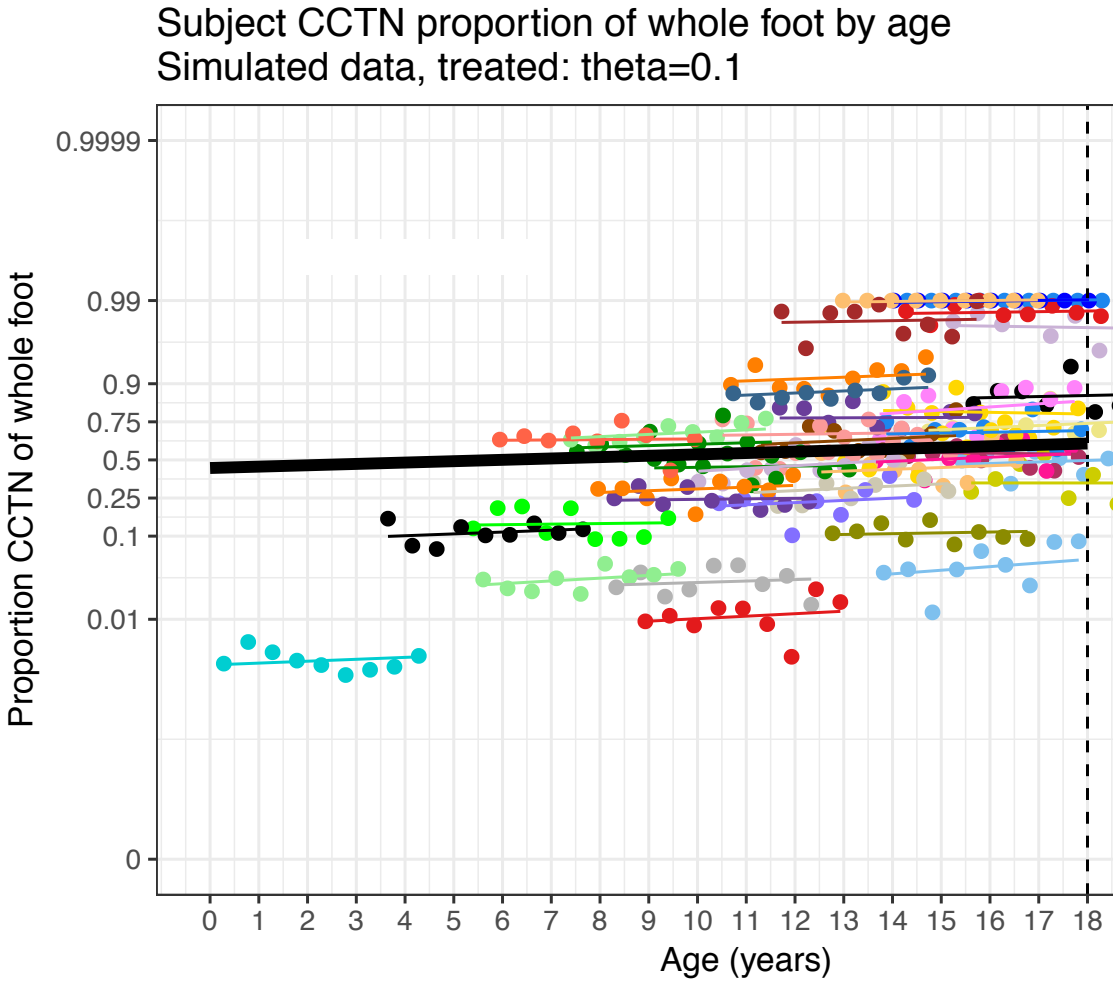

Theta θ	Mean change in proportion CCTN of whole foot per year*
1	0.032
0.9	0.029
0.8	0.026
0.7	0.024
0.6	0.020
0.5	0.017
0.4	0.014
0.3	0.010
0.2	0.007
0.1	0.004
0	0.000

*based on 10,000 simulated trials

Bayesian disease progression model (DPM)

Primary analysis

For each subject, s, at visit, i, assume:

Quantifies rate of disease progression

$$logit(CCTN) \sim Normal(\mu_s, \sigma^2)$$

$$\mu_s = \alpha_s + \beta_s Age_{s,0} + \gamma\beta_s(Age_{s,i} - Age_{s,0})$$

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Test Pr($\gamma < 1$) ≥ 0.994*

* This threshold, found via simulation ensures 2.5% Type I error control

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This model integrates NHS patients into the analysis and allows for differential length of follow up

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Priors

$$\alpha_s \sim Normal(\mu_\alpha, \sigma_\alpha^2) \qquad \mu_\alpha \sim Normal(-3, 1^2) \qquad \sigma_\alpha \sim Uniform(0, 10)$$

$$\beta_s \sim Gamma\left(\frac{\mu_\beta^2}{\sigma_\beta^2}, \frac{\mu_\beta}{\sigma_\beta^2}\right) \qquad \mu_\beta \sim Gamma(0.3^2, 0.3) \qquad \sigma_\beta \sim Uniform(0, 1)$$

$$\sigma \sim Uniform(0, 10)$$

$$\gamma \sim Uniform(0, 2)$$

This model integrates NHS patients into the analysis and allows for differential length of follow up

Test $Pr(\gamma < 1) \geq 0.994$*

* This threshold, found via simulation, ensures 2.5% Type I error control

Trial operating characteristics

$\Pr(\gamma < 1) \geq 0.994$*

Rate of disease progression, γ	4 years of follow up on treated patients	
	30 treated feet	40 treated feet
1	0.016	0.026
0.9	0.088	0.15
0.8	0.362	0.46
0.7	0.696	0.796
0.6	0.928	0.968
0.5	0.996	0.998
0.4	>0.999	>0.999
0.3	>0.999	>0.999
0.2	>0.999	>0.999
0.1	>0.999	>0.999
0	>0.999	>0.999

Trial - using Bayesian model

- All natural history data included
- 4 years of follow up for each treated subject
- 53 OR 63 (unique) feet:
  - 23 from natural history
  - 30 OR 40 treated
- Analysis of a single parameter, γ, which quantifies disease progression defined by proportion of whole foot CCTN

*Threshold selected to ensure one-sided 2.5% Type I error control

500 simulations per scenario

Design comparison

OPC vs. DPM

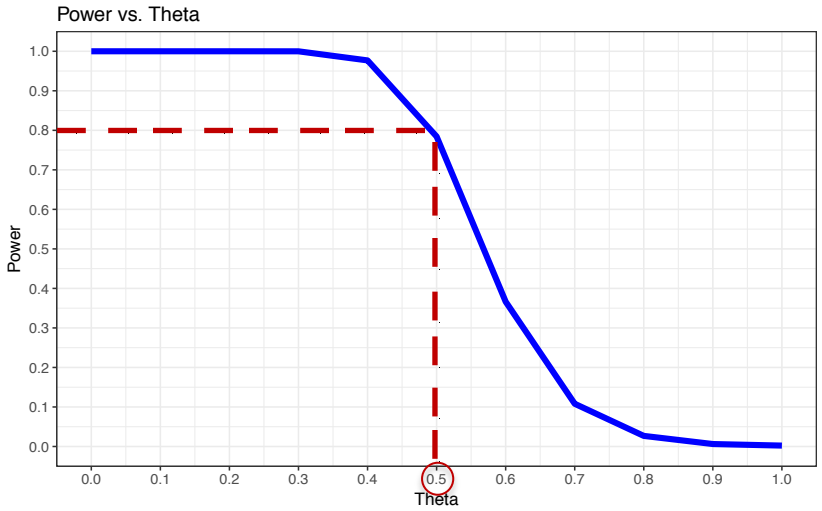
OPC analysis

40 treated feet

4 years of follow up

Analysis of lower confidence bound

Powered to detect a treatment effect equivalent to at least 50% slowing in CCTN progression



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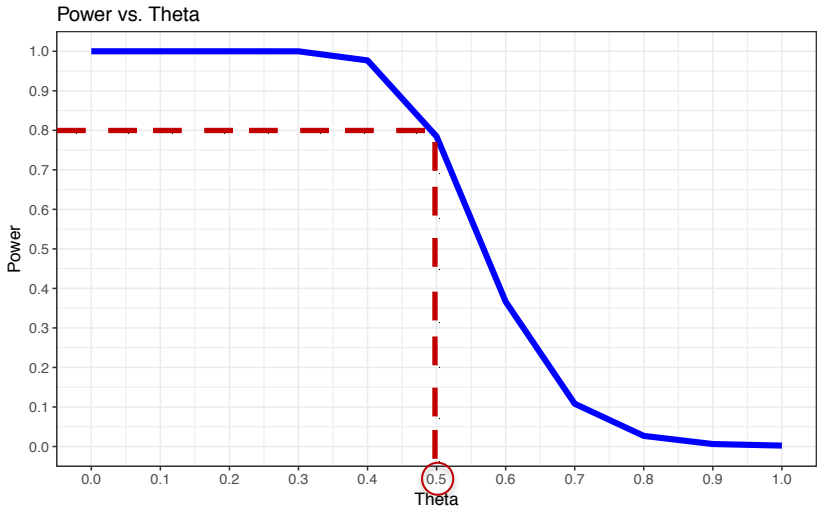

DPM analysis

40 treated feet

4 years of follow up

Analysis of Bayesian disease progression model

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