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

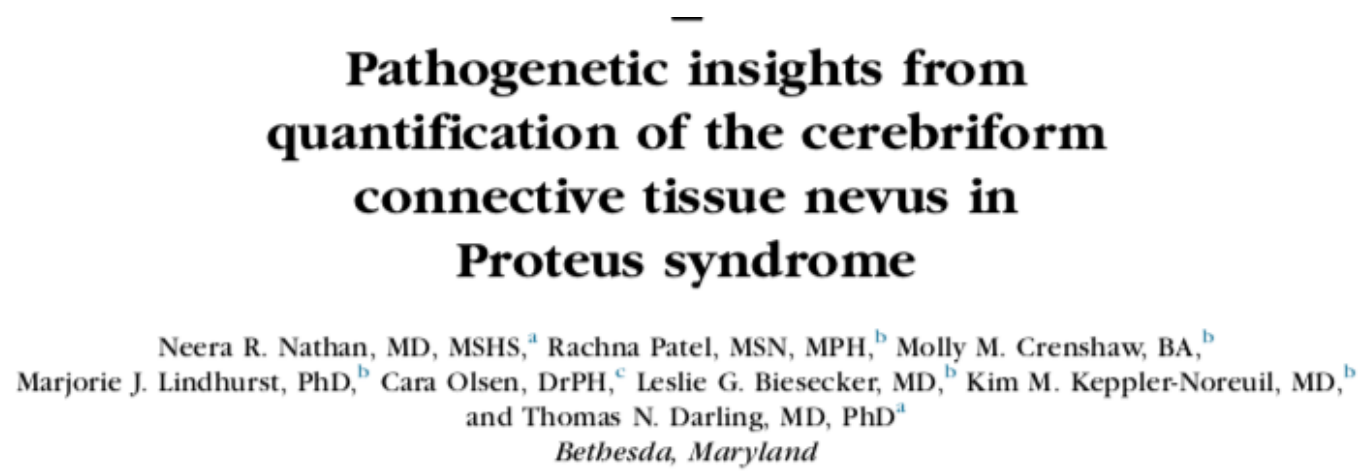
Barbara Wendelberger

WSDS 2019 – Bellevue

4 October 2019

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

Neera R. Nathan, MD, MSHS,[a] Rachna Patel, MSN, MPH,[b] Molly M. Crenshaw, BA,[b] Marjorie J. Lindhurst, PhD,[b] Cara Olsen, DrPH,[c] Leslie G. Biesecker, MD,[b] Kim M. Keppler-Noreuil, MD,[b] and Thomas N. Darling, MD, PhD[a]

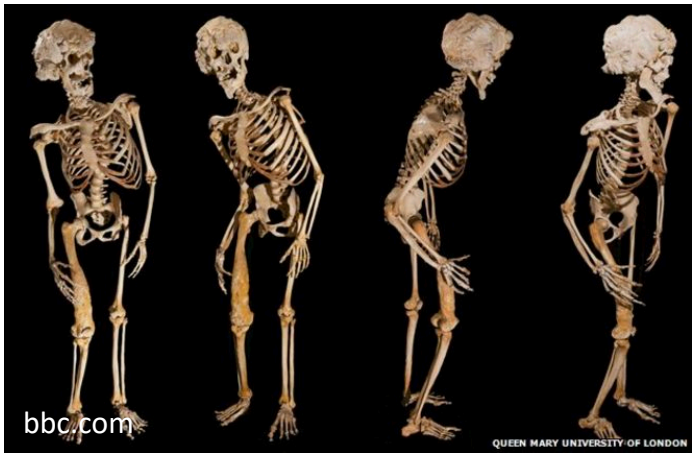
Bethesda, Maryland

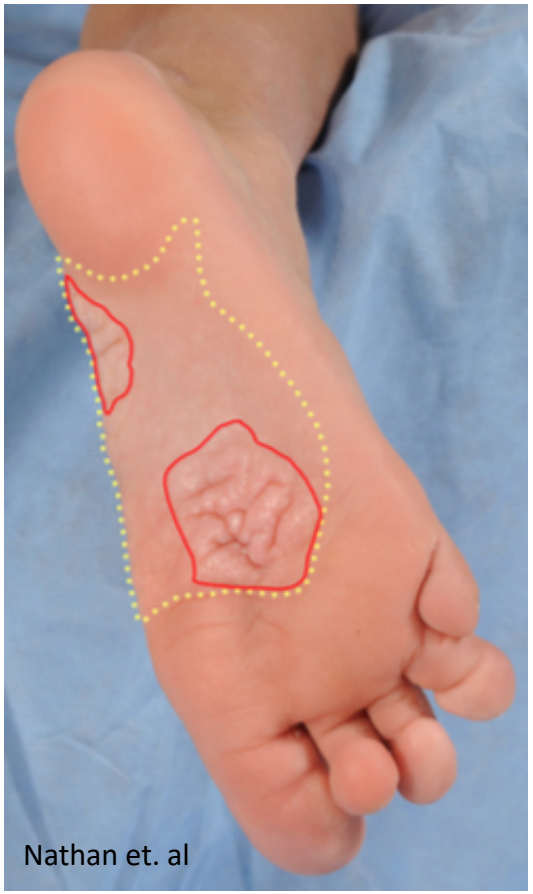
Proteus syndrome

Disease characterization and manifestation

Rare disease

- Result of a genetic mutation
- Manifests as overgrowth of skin, bone, and other tissues
- Plantar cerebriform connective tissue nevus (CCTN) is its most specific symptom



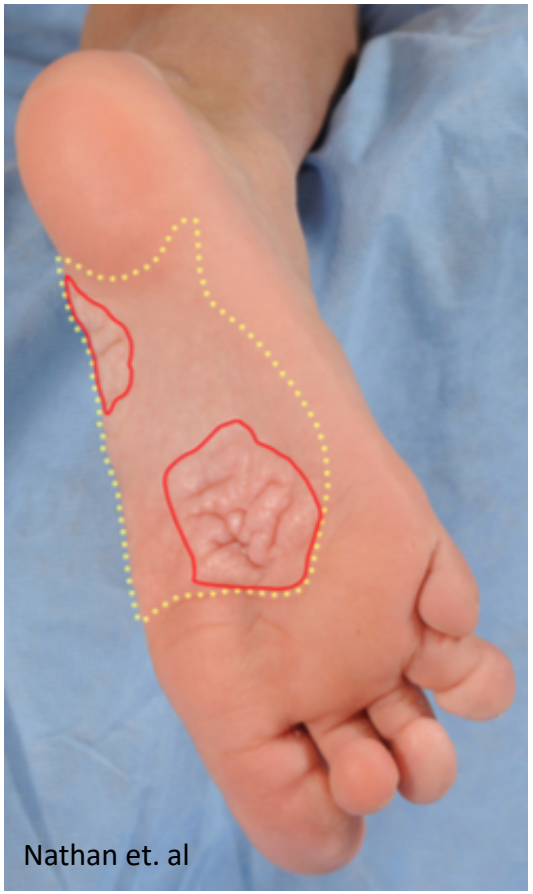


Proteus syndrome

Disease characterization and manifestation

Rare Disease

- Cause
- Definition
- Symptoms



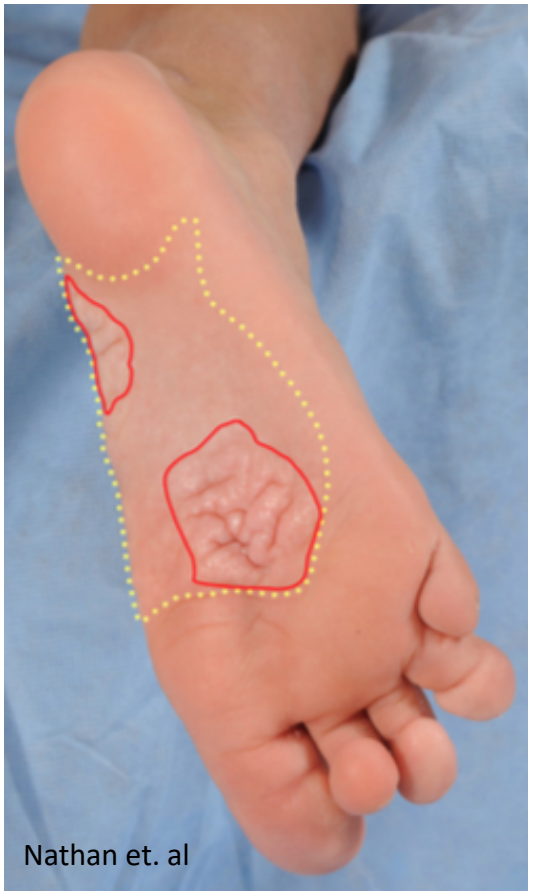
Proteus syndrome

Disease characterization and manifestation

Rare Disease
- Cause
- Definition
- Symptoms

?

Treatment/Cure

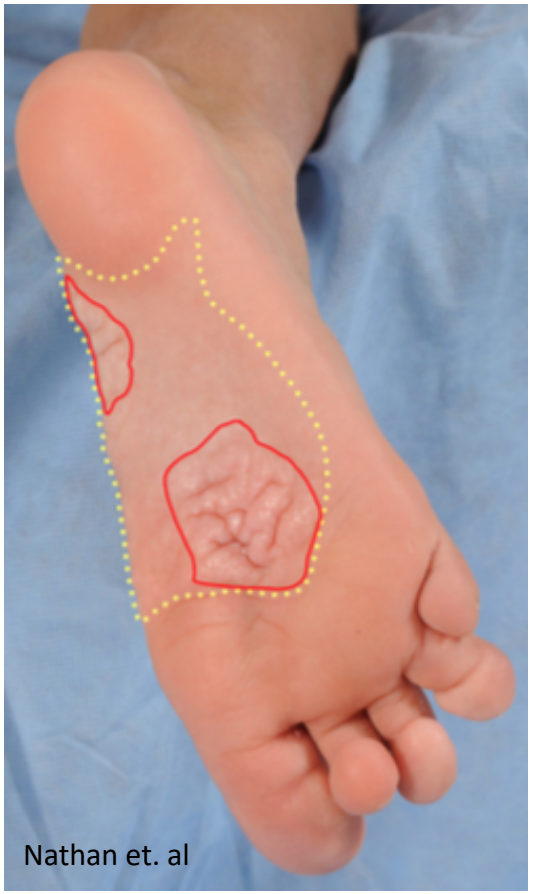


Clinical trial design

Rare disease

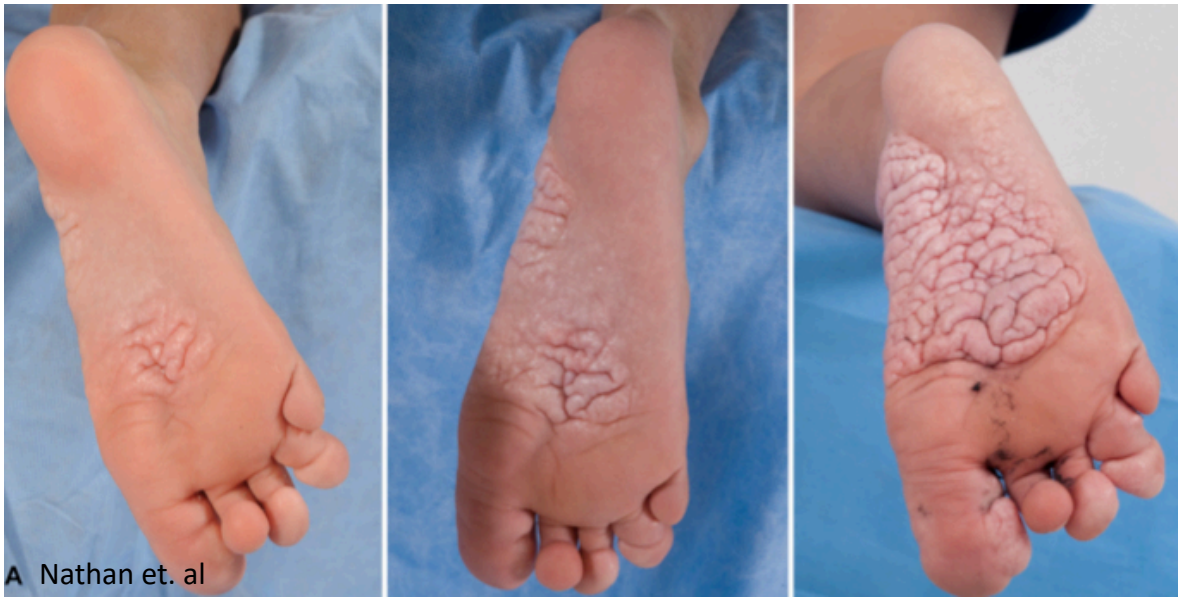
Challenges in a rare disease

- Small, heterogenous patient populations
- Insufficient understanding of disease etiology
- Poorly developed study endpoints



Natural history study (NHS)

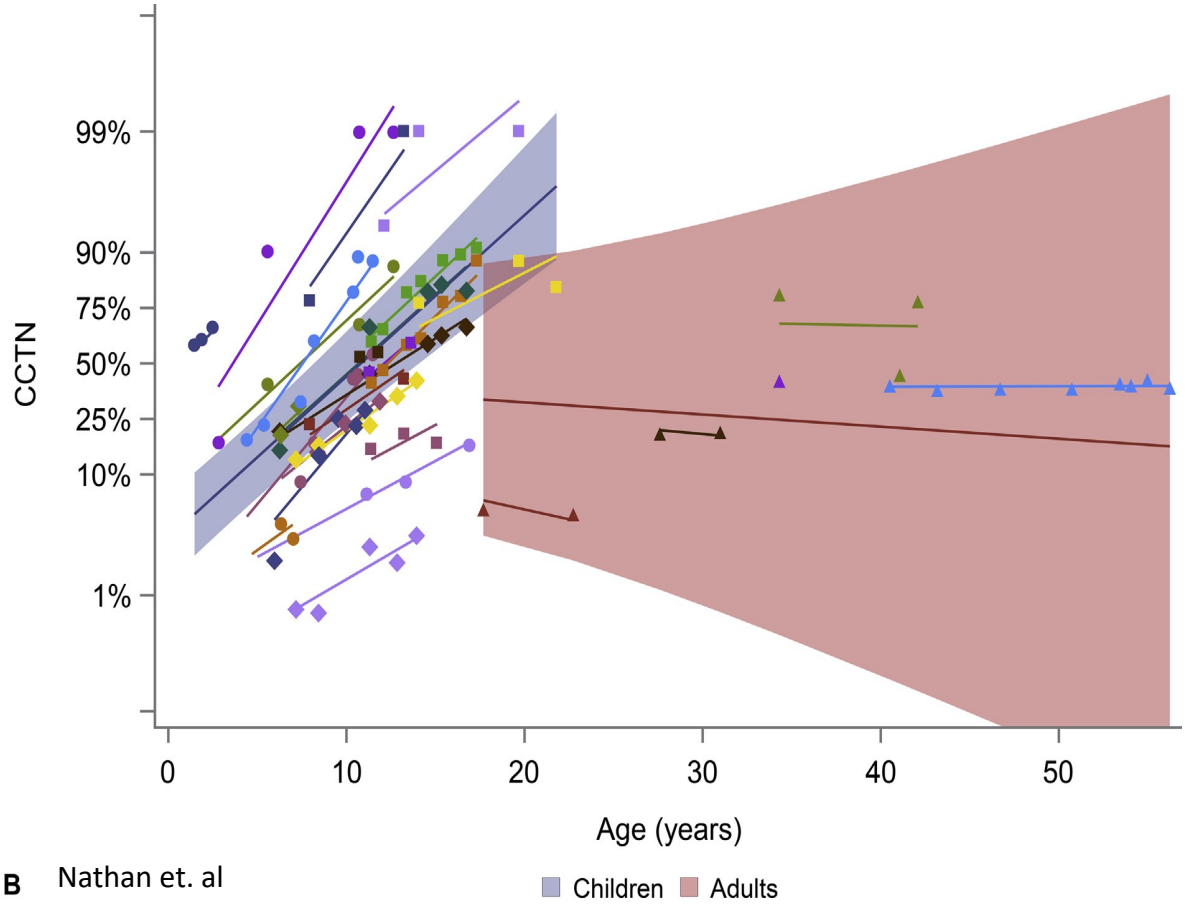
Proteus syndrome



Collect observational data on the natural trajectory of disease

Natural history study (NHS)

Proteus syndrome

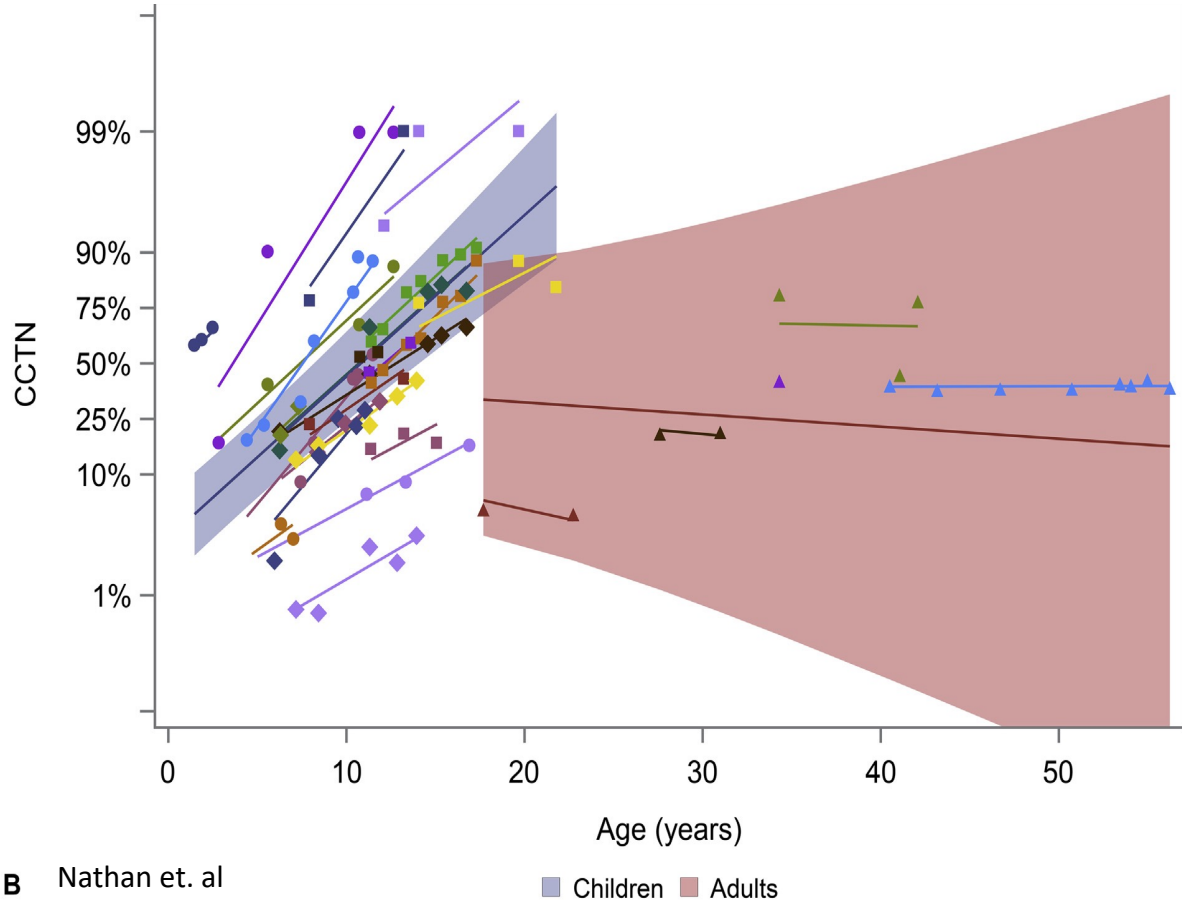


Disease progression

B Nathan et. al

Natural history study (NHS)

Proteus syndrome



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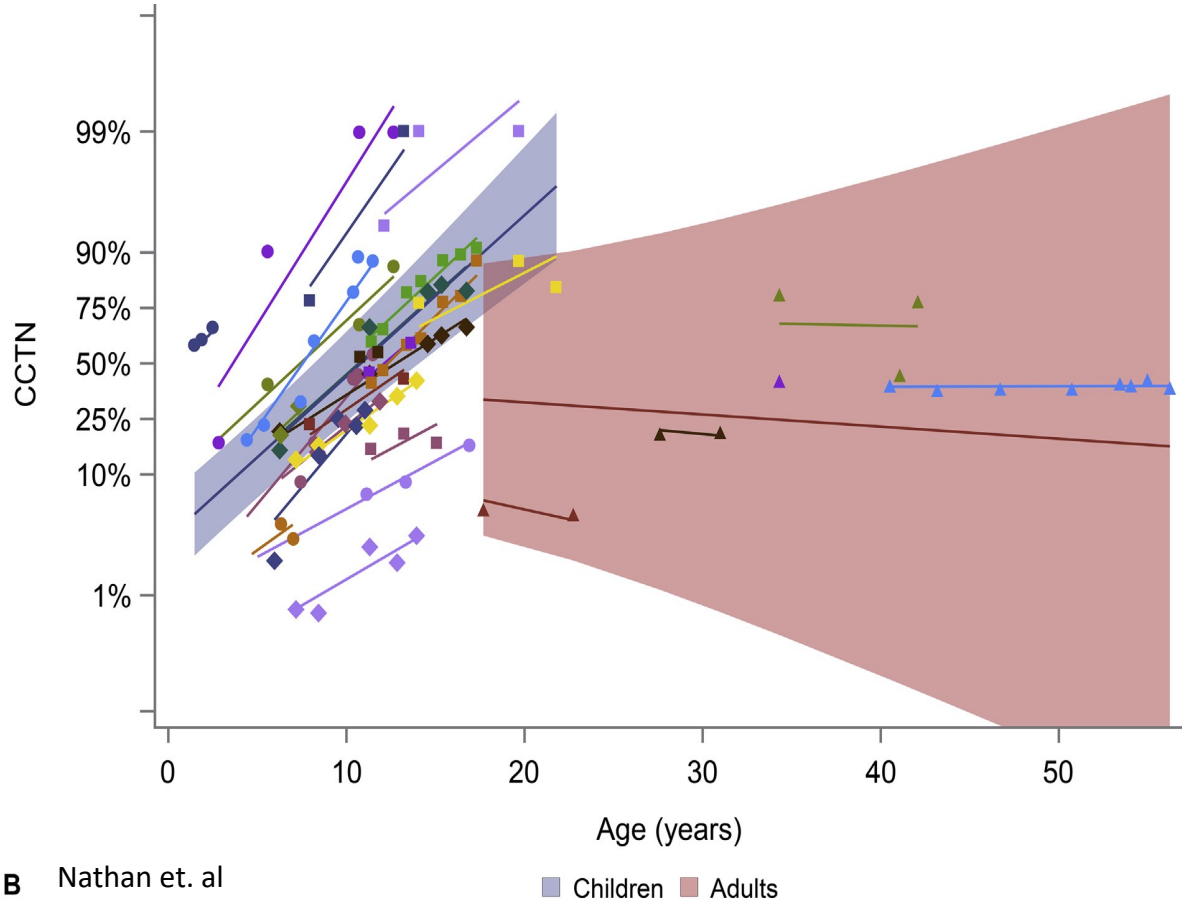
Disease progression

- measurable endpoint

Natural history study (NHS)

Proteus syndrome



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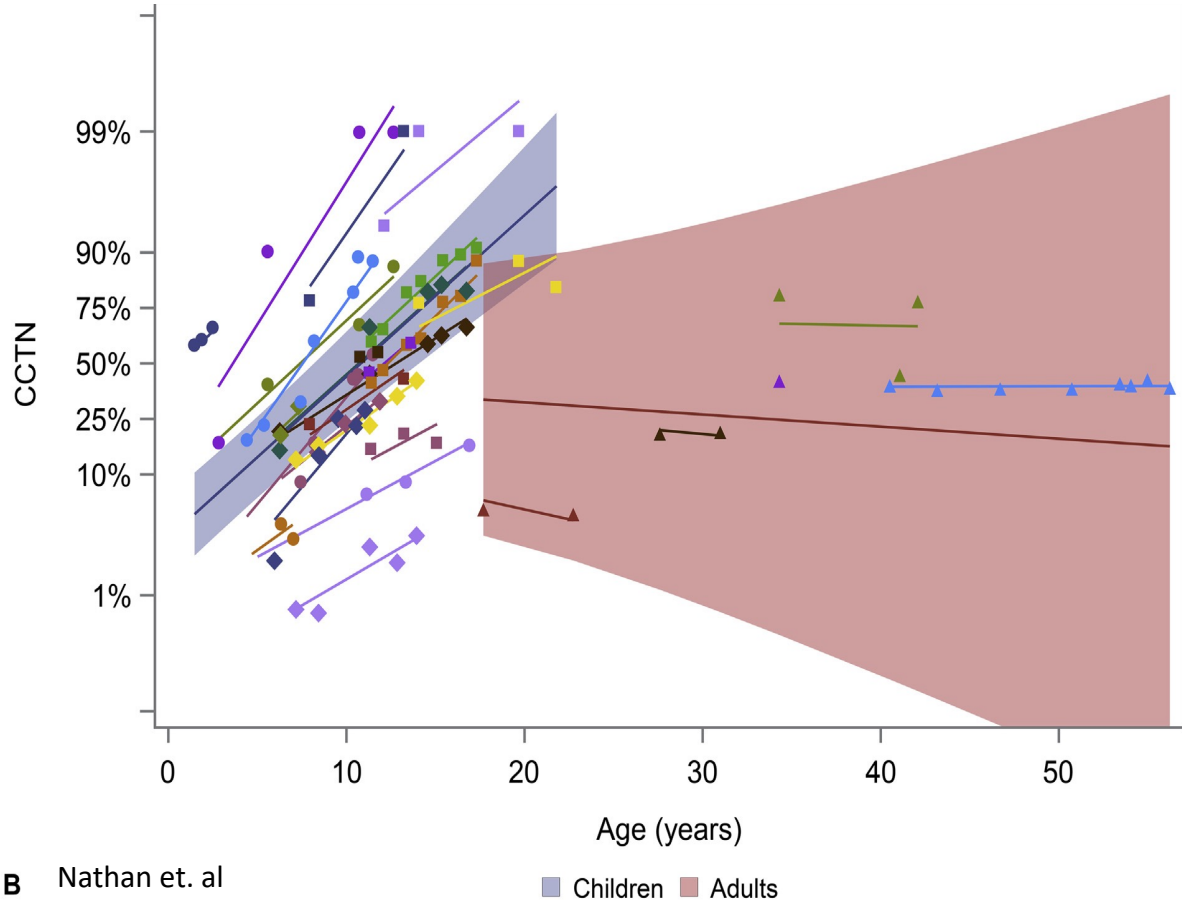
Disease progression

- measurable endpoint
- a function of age

Natural history study (NHS)

Proteus syndrome



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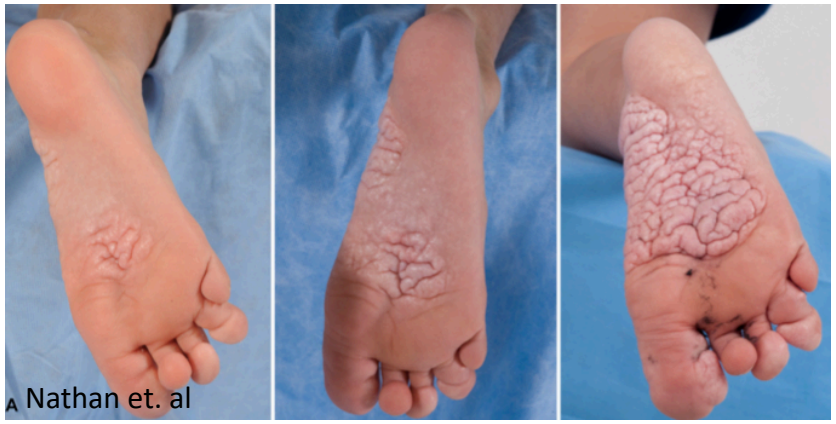
Disease progression

- measurable endpoint
- a function of age
- pediatric vs. adult

Natural history study

Pediatric CCTN disease progression

Longitudinal observations



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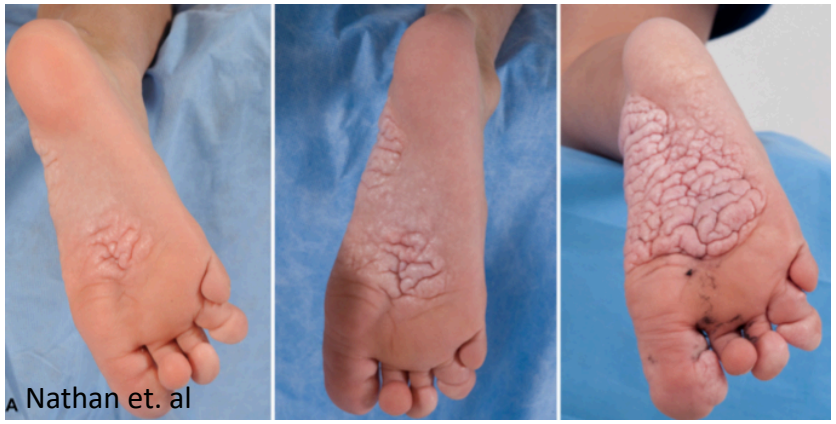

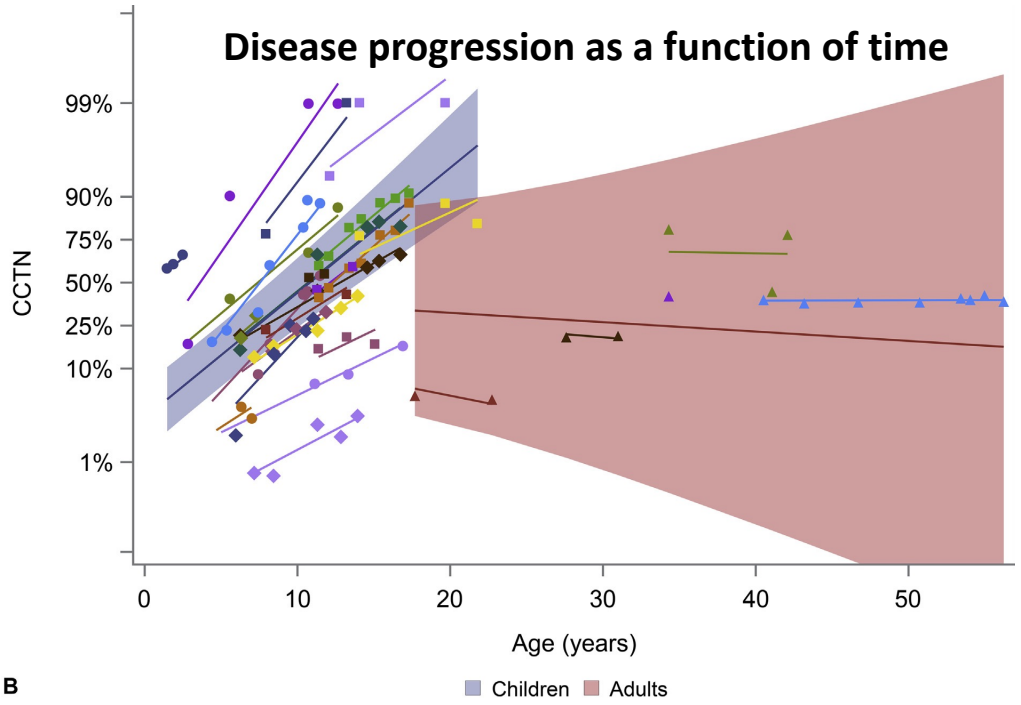

Natural history study

Pediatric CCTN disease progression

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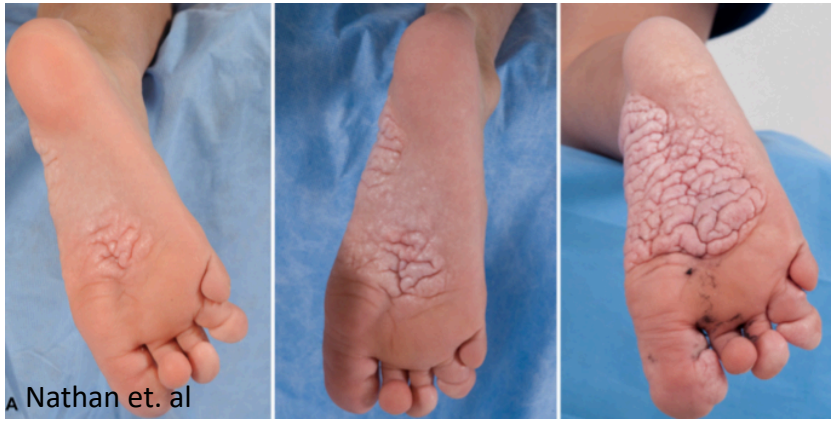
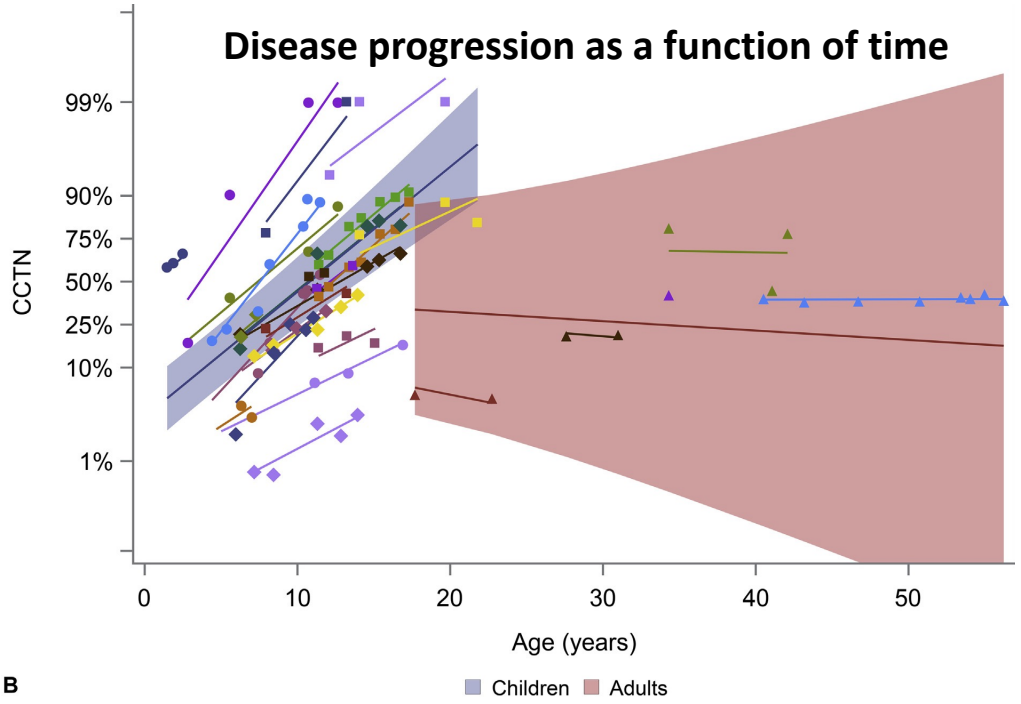


Can we leverage data from this natural history study (NHS) to:

-understand natural rate of progression



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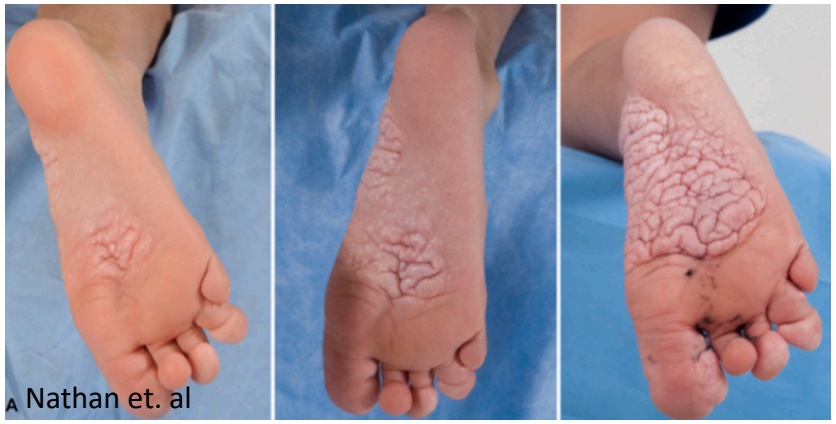

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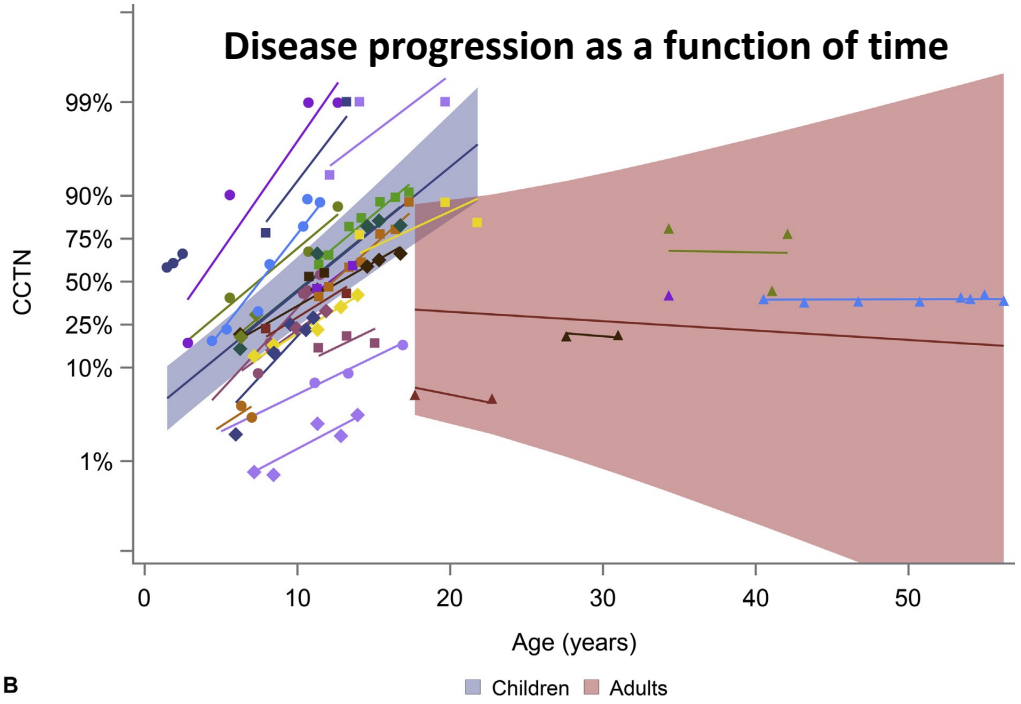
-create a virtual subject simulator



Natural history study

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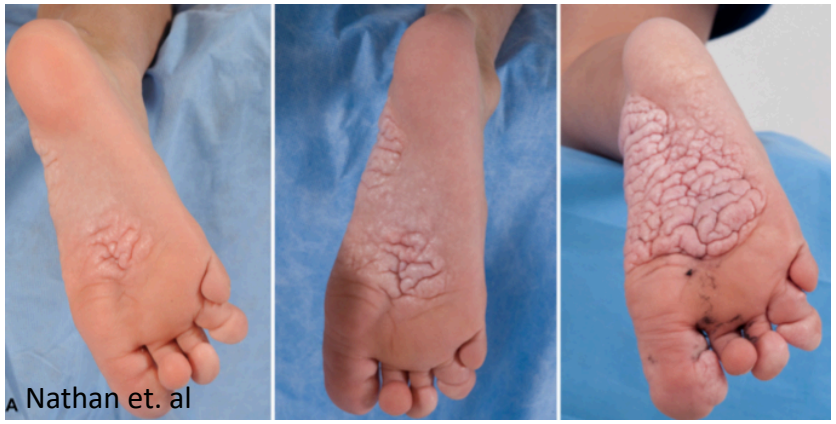
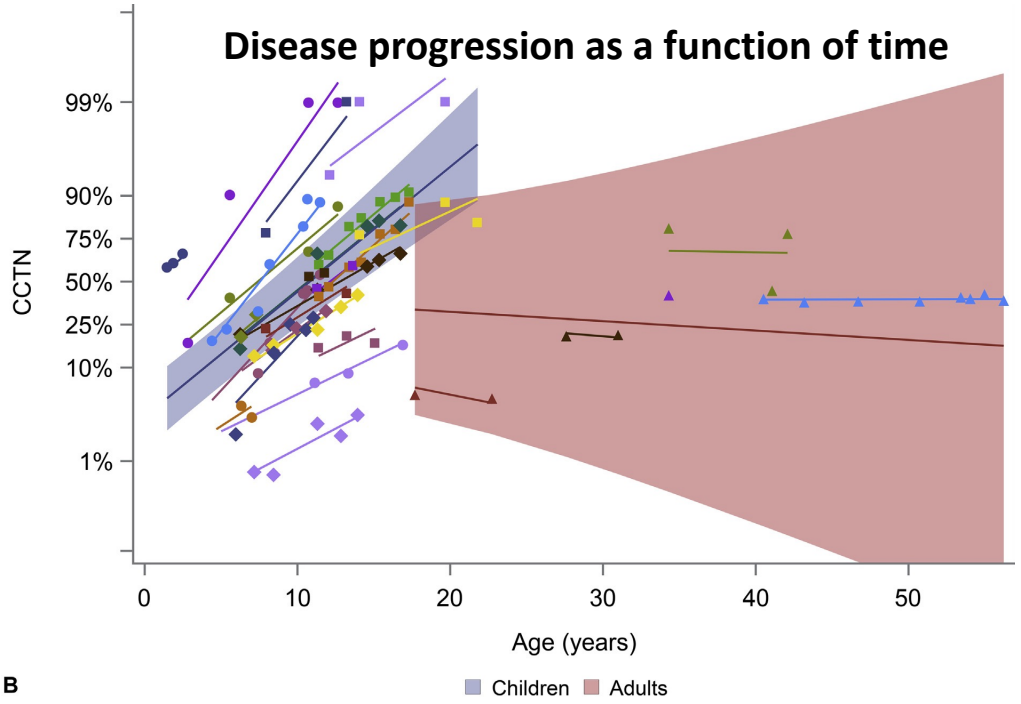


Can we leverage data from this natural history study (NHS) to:

-understand natural rate of progression
-create a virtual subject simulator
-simulate a treatment effect



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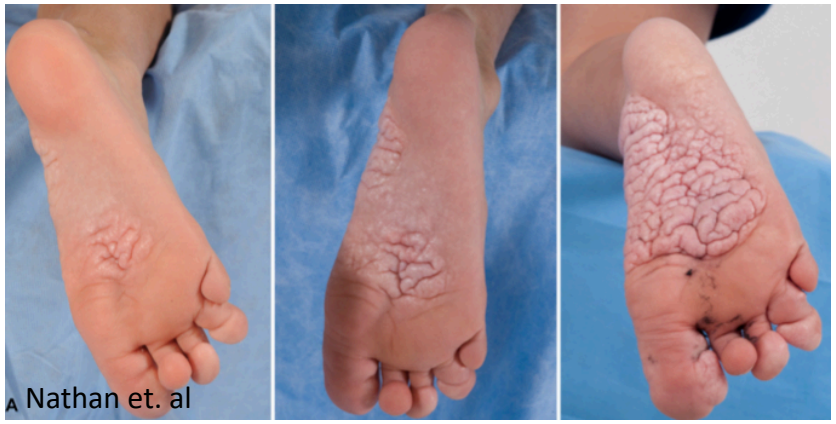

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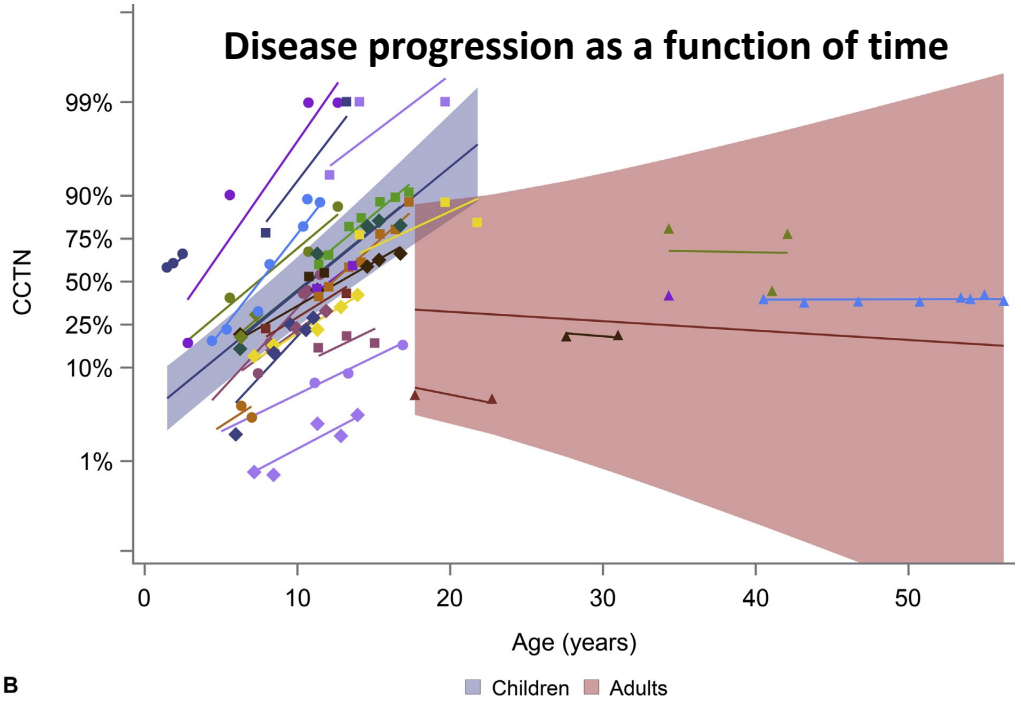

Natural history study

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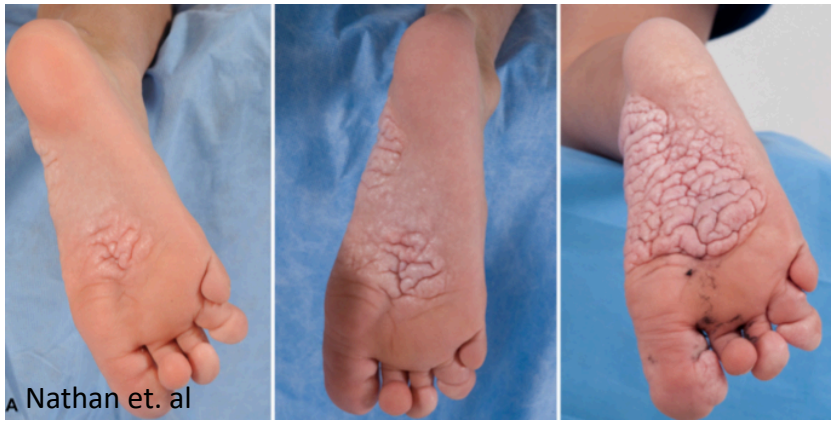
Longitudinal observations



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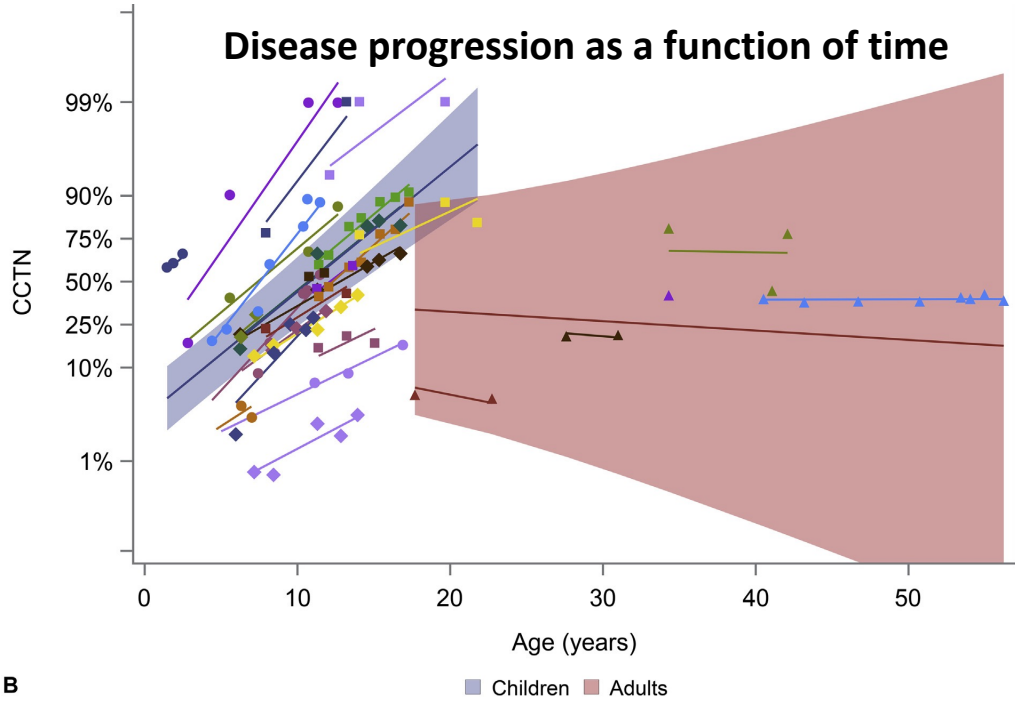
-understand natural rate of progression
-create a virtual subject simulator
-simulate a treatment effect
-build a Bayesian disease progression model (DPM)
-design a single arm trial that
  - compares disease progression of treated patients to NHS
  - defines a final analysis using the DPM



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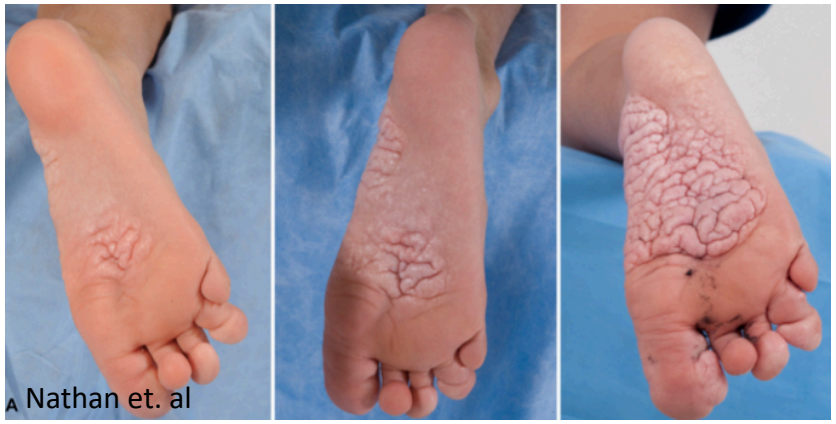

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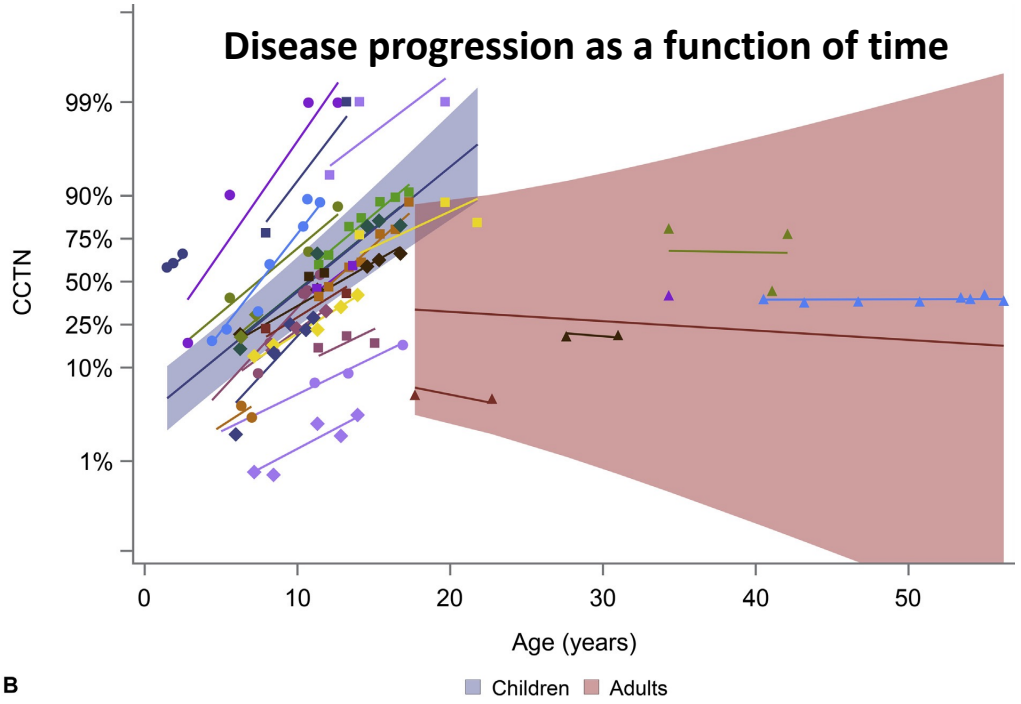
-understand natural rate of progression
-create a virtual subject simulator
-simulate a treatment effect
-build a Bayesian disease progression model (DPM)
-design a single arm trial that
  - compares disease progression of treated patients to NHS
  - defines a final analysis using the DPM
-understand the operating characteristics of this design

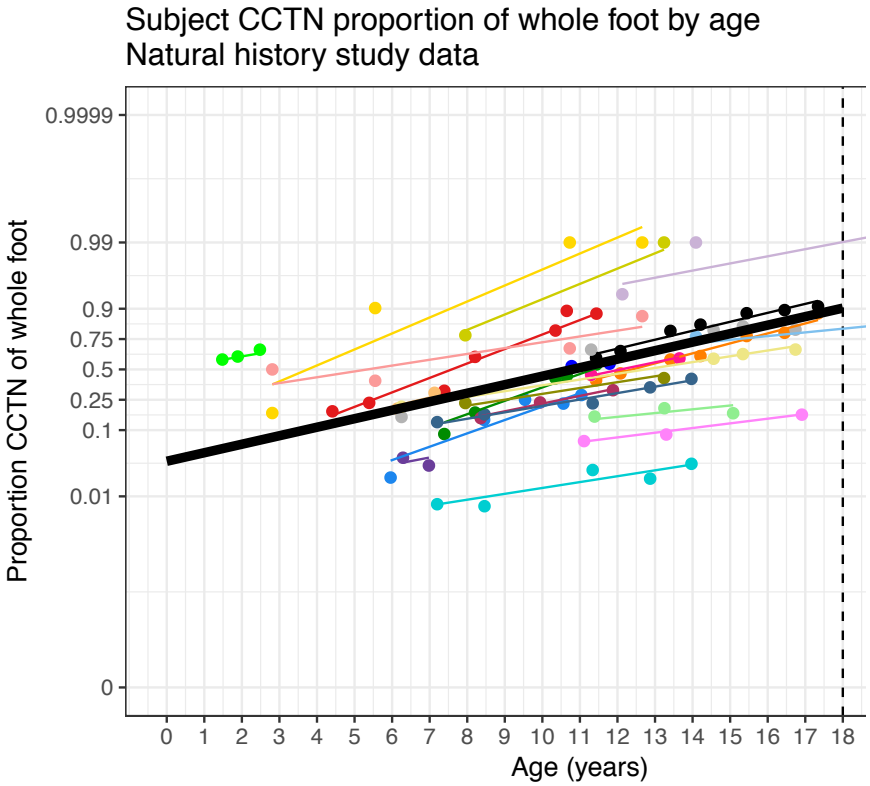


Natural history study

Understand natural rate of 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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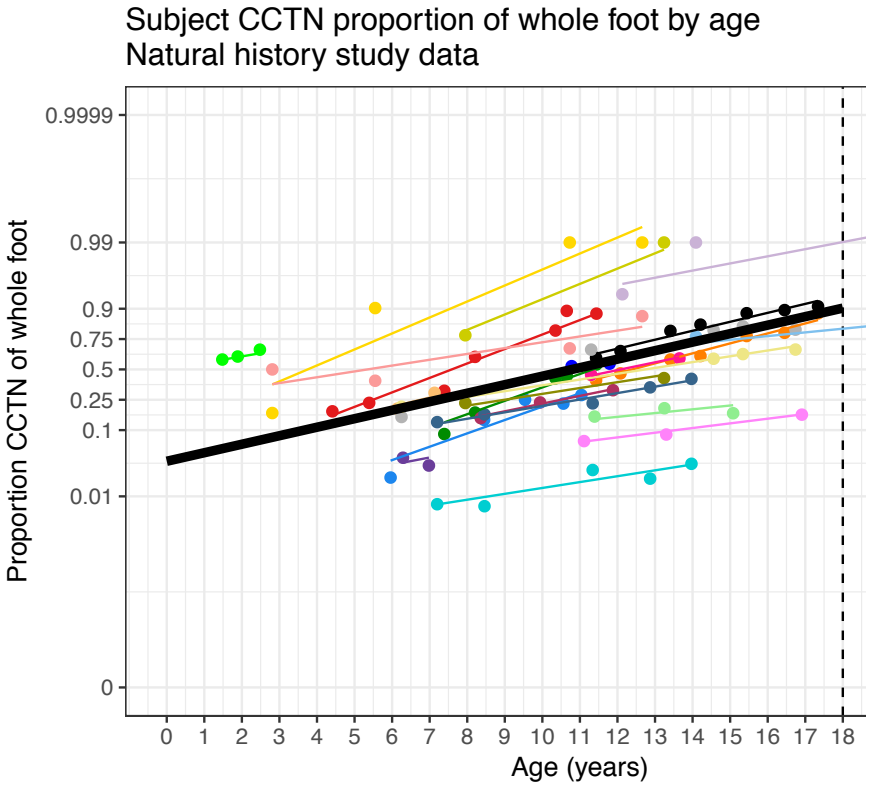

Estimates:

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} : variance residual error

CCTN simulation model

Virtual patient simulator

Use mixed model estimates to simulate virtual patients

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

Natural history of disease progression

CCTN simulation model

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Use mixed model estimates to simulate virtual patients

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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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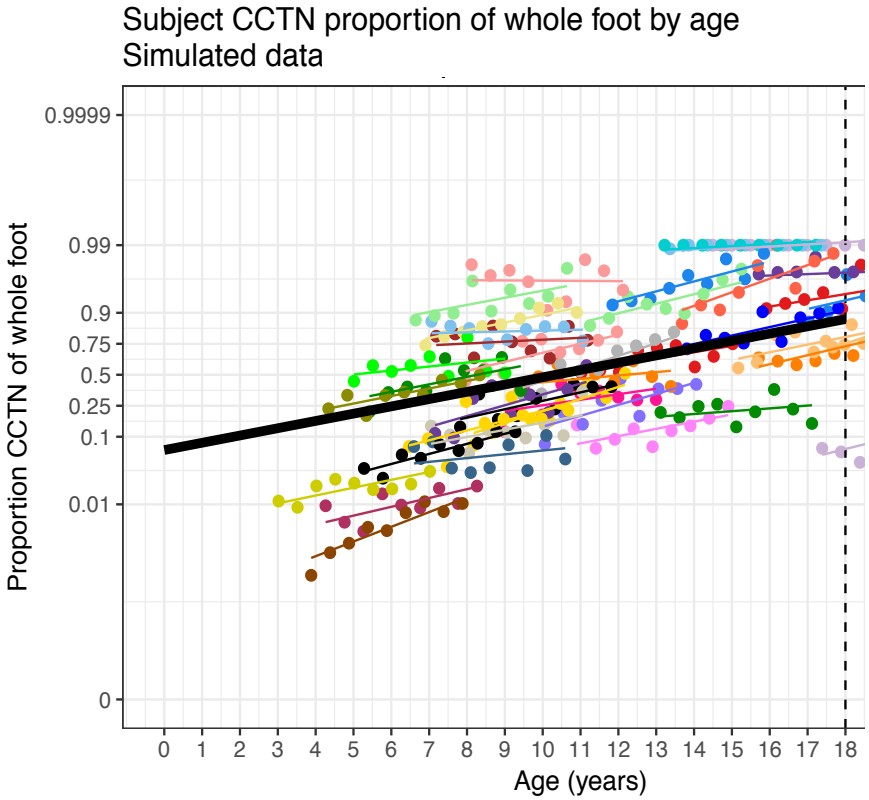

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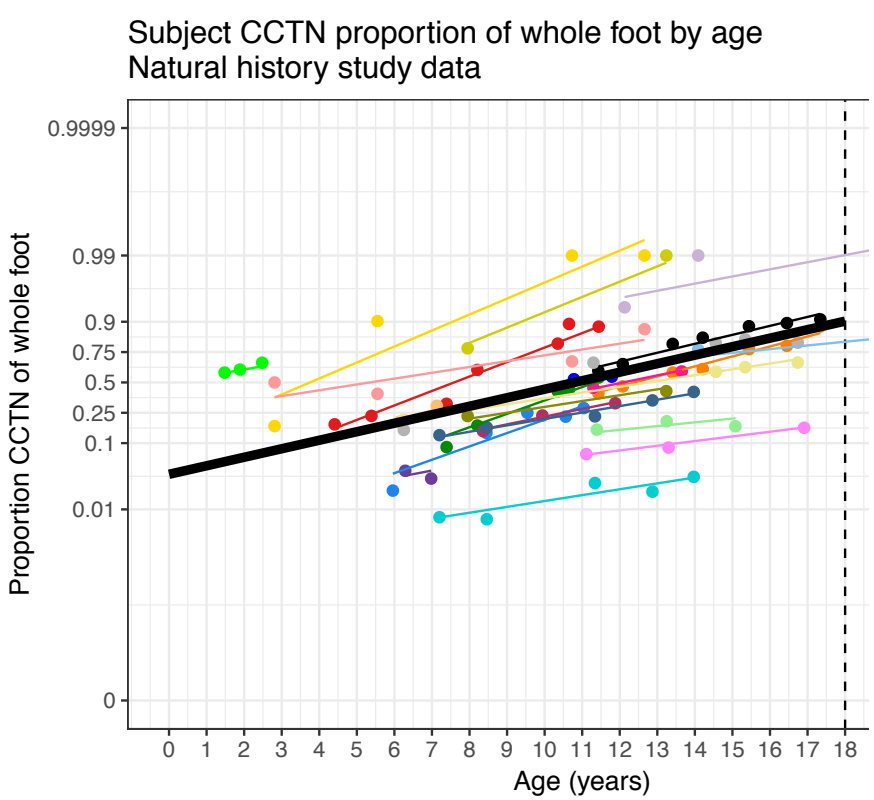
$$\varepsilon_{si} \sim Normal(0, \sigma^2_{\varepsilon})$$

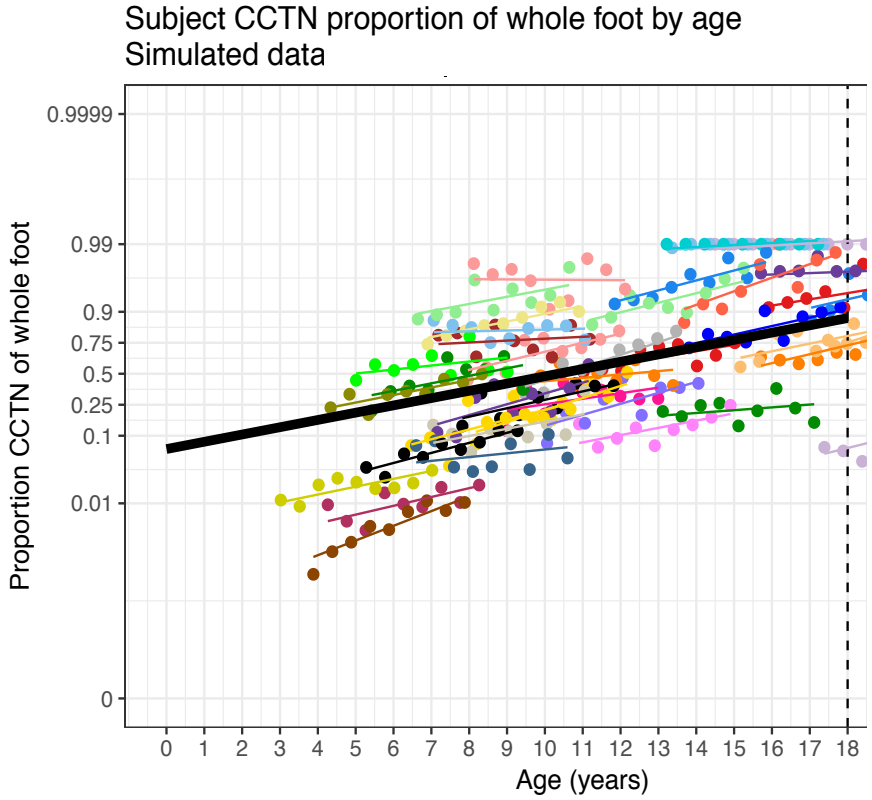
Use mixed model parameter estimates to create a virtual patient simulator that can generate patients with the same characteristics as the NHS patients

Assume that baseline age is distributed as a truncated normal.

CCTN simulation model

Virtual patient simulator

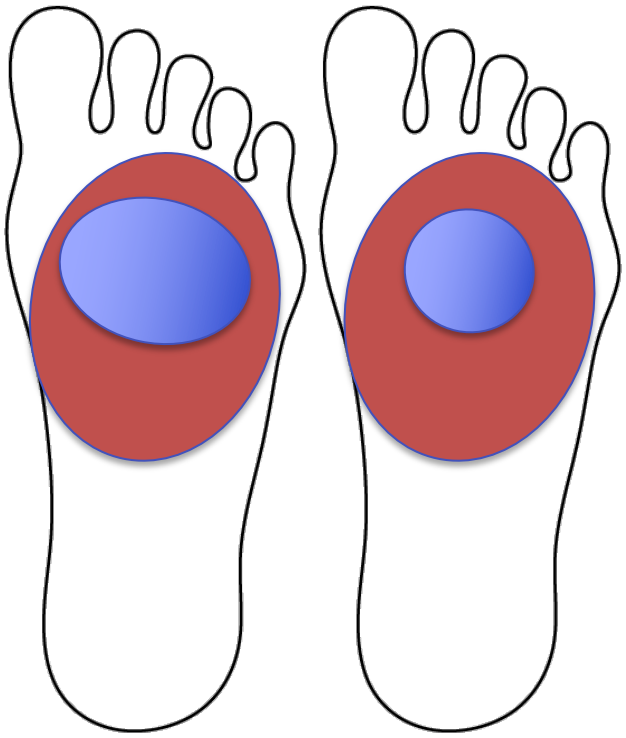




Simulating a treatment effect

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

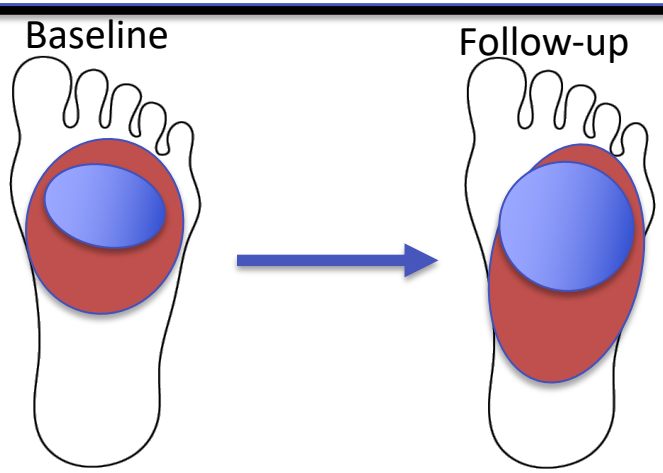


Untreated Treated

Treatment effect on more than CCTN?

Projection Based on Natural History

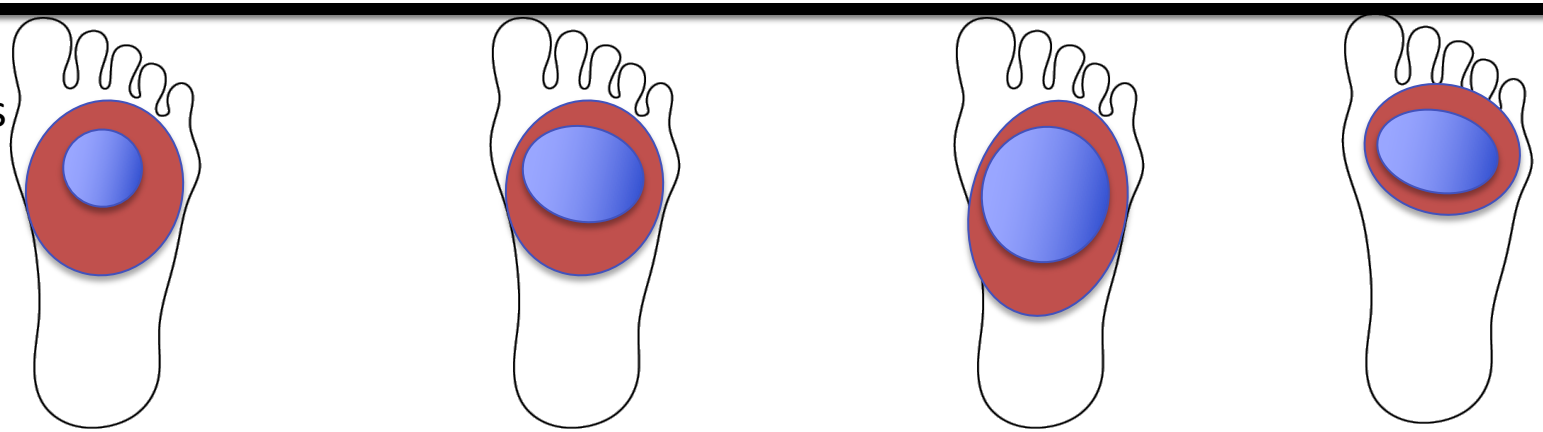
UNTREATED



CCTN: Increase
Abnormal skin: Increase
Confluent papules and nodules: Increase

Possible Scenarios

TREATED



CCTN: Reduced
Ab. skin: Same
Con. papules: Increased

CCTN: Increased, slowed
Ab. skin: Same
Con. papules: Reduced

CCTN: Increased
Ab. skin: Increased
Con. papules: Same

CCTN: Same
Ab. skin: Reduced
Con. papules: Reduced

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

$$X_{s,i} = Age\ of\ subject\ s\ at\ visit\ i$$
$$t_s = Age\ of\ subject\ s\ when\ treated$$

Natural history of disease progression

$$logit(CCTN_{si}) = \begin{cases} \beta_{0,s} + \beta_{1,s}X_{s,i} + \epsilon_{si} & X_{s,i} \leq t_s \end{cases}$$

Simulating a treatment effect

Proportional slowing of CCTN progression

- Treatment effect, $\boldsymbol{\theta}$, is applied to the slope parameter of the simulation model
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Natural history of disease progression

Natural history of disease progression

Years treated

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

$X_{s,i} = Age\ of\ subject\ s\ at\ visit\ i$

$t_s = Age\ of\ subject\ s\ when\ treated$

$$logit(CCTN_{si}) = \begin{cases} \beta_{0,s} + \beta_{1,s}X_{s,i} + \epsilon_{si} & X_{s,i} \le t_s \\ \beta_{0,s} + \beta_{1,s}t_s + \theta\beta_{1,s}(X_{s,i} - t_s) + \epsilon_{si} & X_{s,i} > t_s \end{cases}$$

Natural history of disease progression

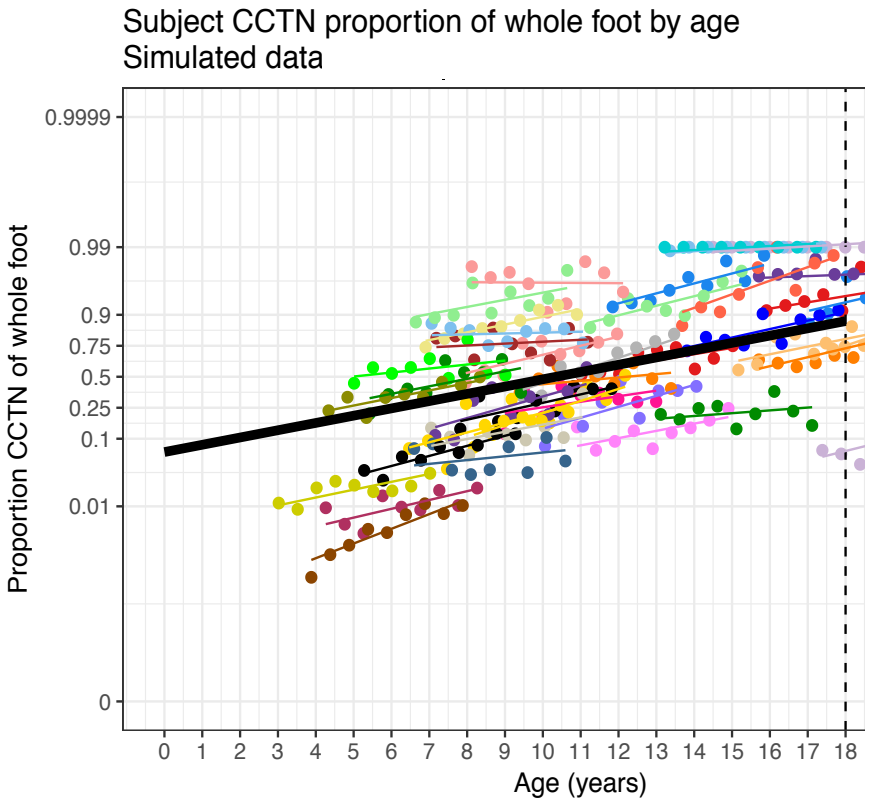
Natural history of disease progression

Years treated

Treated disease progression

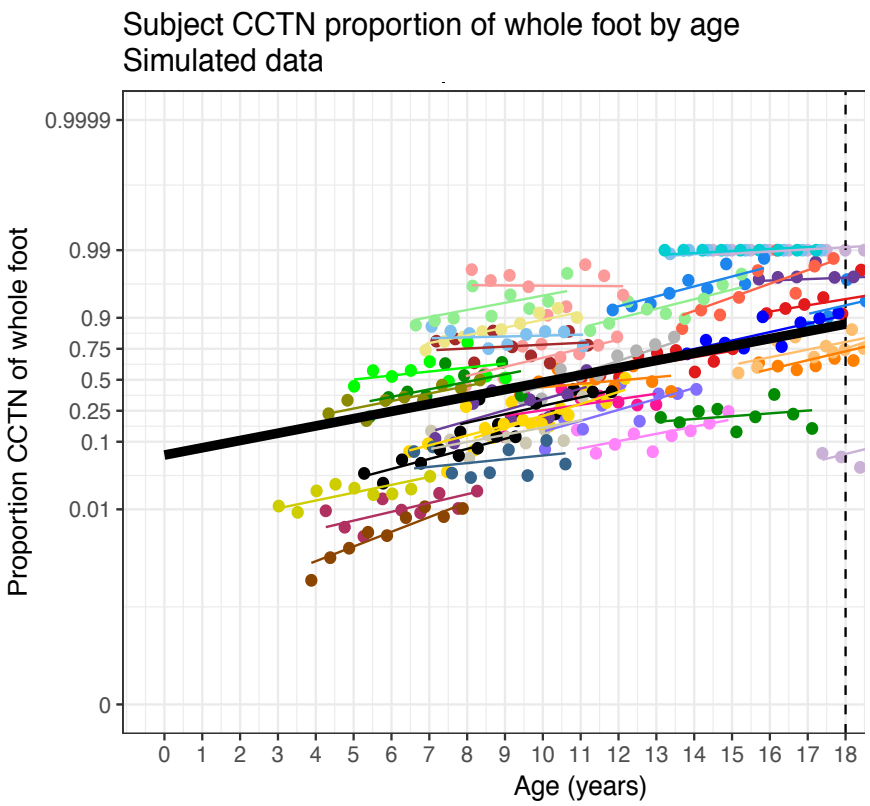
Simulating a treatment effect

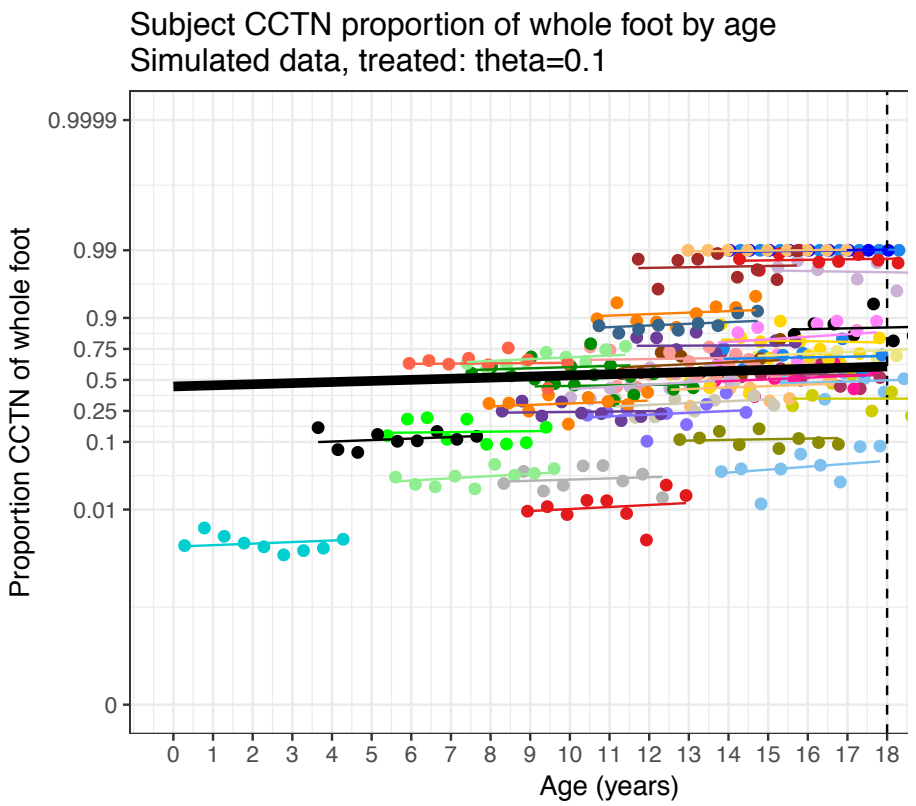
Proportional slowing of CCTN progression



Simulating a treatment effect

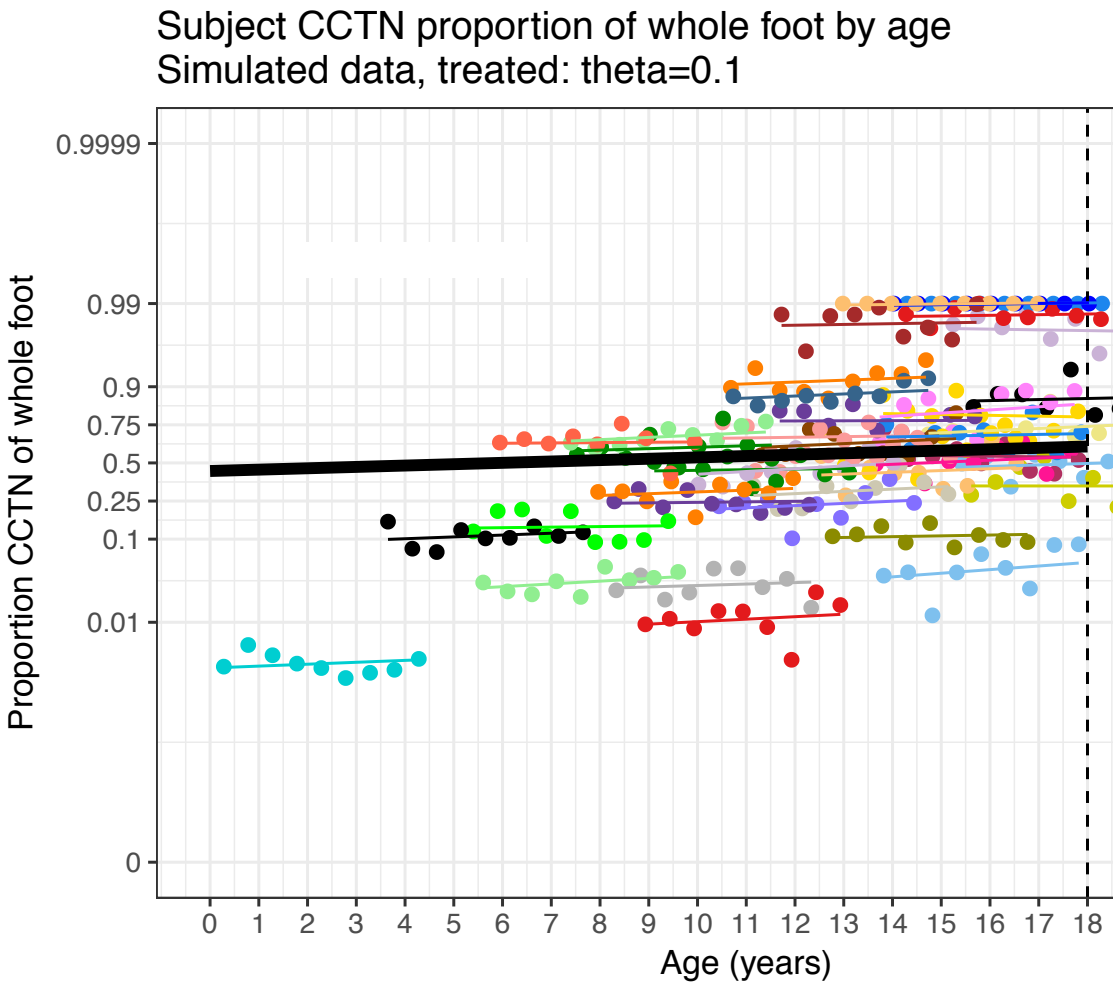
Proportional slowing of CCTN progression





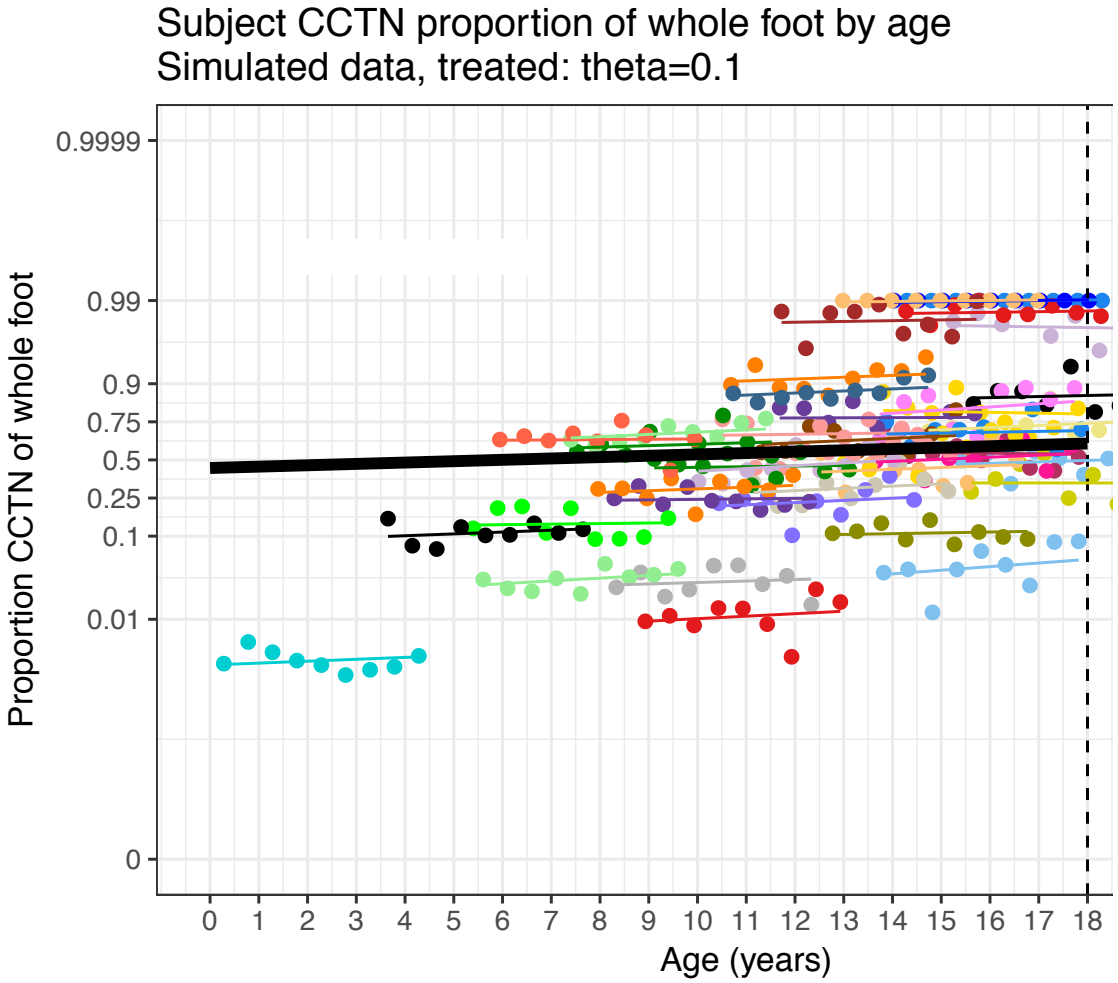
Simulating a treatment effect

Proportional slowing of CCTN progression



Simulating a treatment effect

Proportional slowing of CCTN progression



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

Analysis model

Bayesian disease progression model

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

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

$$\mu_s = \begin{cases} \alpha_s + \beta_s X_{s,i} & X_{s,i} \leq t_s \\ \alpha_s + \beta_s t_s + \gamma \beta_s (X_{s,i} - t_s) & X_{s,i} > t_s \end{cases}$$

Where: $X_{s,i} = Age\ of\ subject\ s\ at\ visit\ i$

$t_s = Age\ of\ subject\ s\ when\ treated$

Quantifies change in rate of disease progression

Analysis model

Bayesian disease progression model

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

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

$$\mu_s = \begin{cases} \alpha_s + \beta_s X_{s,i} & X_{s,i} \leq t_s \\ \alpha_s + \beta_s t_s + \gamma \beta_s (X_{s,i} - t_s) & X_{s,i} > t_s \end{cases}$$

Where: $X_{s,i} = Age\ of\ subject\ s\ at\ visit\ i$

$t_s = Age\ of\ subject\ s\ when\ treated$

Quantifies change in rate of disease progression

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

Analysis model

Bayesian disease progression model

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

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

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Quantifies change in rate of disease progression

Priors

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

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

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

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

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

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

Test $Pr(\gamma < 1) \ge 0.975$*

* Correct threshold to ensure Type I error control will be found via simulation

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

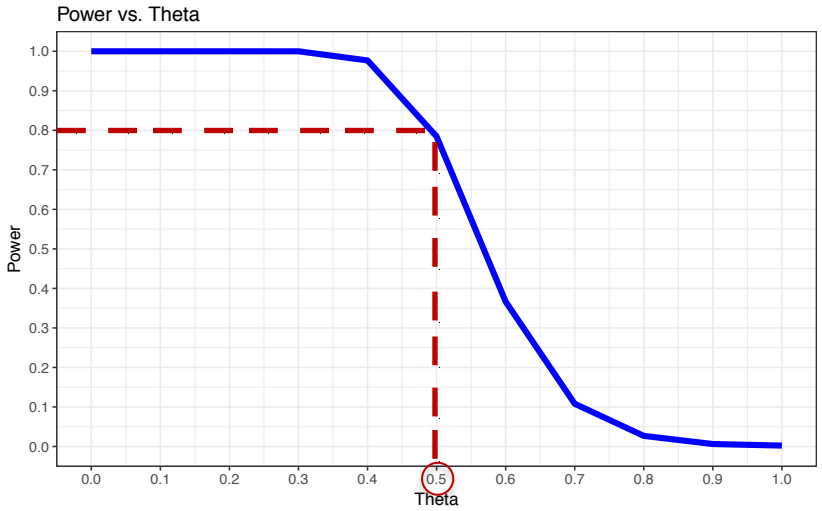
OPC analysis

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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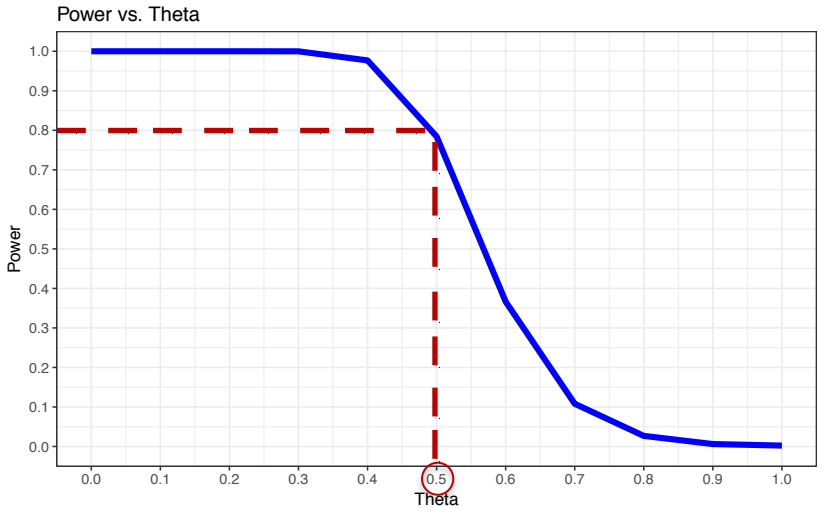

DPM analysis

40 treated feet

4 years of follow up

Analysis of Bayesian disease progression model

Powered to detect a treatment effect equivalent to at least 30% slowing in CCTN progression