Population Approach Group in Europe
PAGE– Stockholm– June 12, 2019

A disease progression model for geographic atrophy

Pascal Chanu, Pharm.D.
Senior Modeling & Simulation Expert
Clinical Pharmacology, Genentech/Roche, France

Marchand M, Vadhavkar S, Maass K, Gow J, Deng R, Jin J, Quartino A

Through the eyes of a person with geographic atrophy (GA)

Roche

Roche and City University London

https://www.youtube.com/watch?v=Lj3-L0ZU0ZU

Snapshot on Geographic Atrophy

A CLOSER LOOK AT ADVANCED AMD

Age-related macular degeneration (AMD) is a leading cause of blindness in people age 50 and older. ***Geographic atrophy****, an advanced form of AMD, can have a devastating impact on vision.*[1]

An Unmet Need

More than **5 million** people worldwide have geographic atrophy,[2]

including nearly **1 million** people in the U.S.[7]

In developed nations, approximately **1 in 29** people over **age 75** have geographic atrophy, [3,4,5]

which increases to nearly **1 in 4** people over **age 90**.[6]

Family History and Other AMD Risk Factors[1]

Genetics – a family history increases the risk of AMD

With family history: **50% risk**
No family history: **12% risk**[12]

A recent study identified **19 genetic markers** associated with AMD risk[13]

Other AMD risk factors:

AGE

SMOKING NEARLY DOUBLES THE RISK

OBESITY INCREASES THE RISK FOR ADVANCED AMD[14]

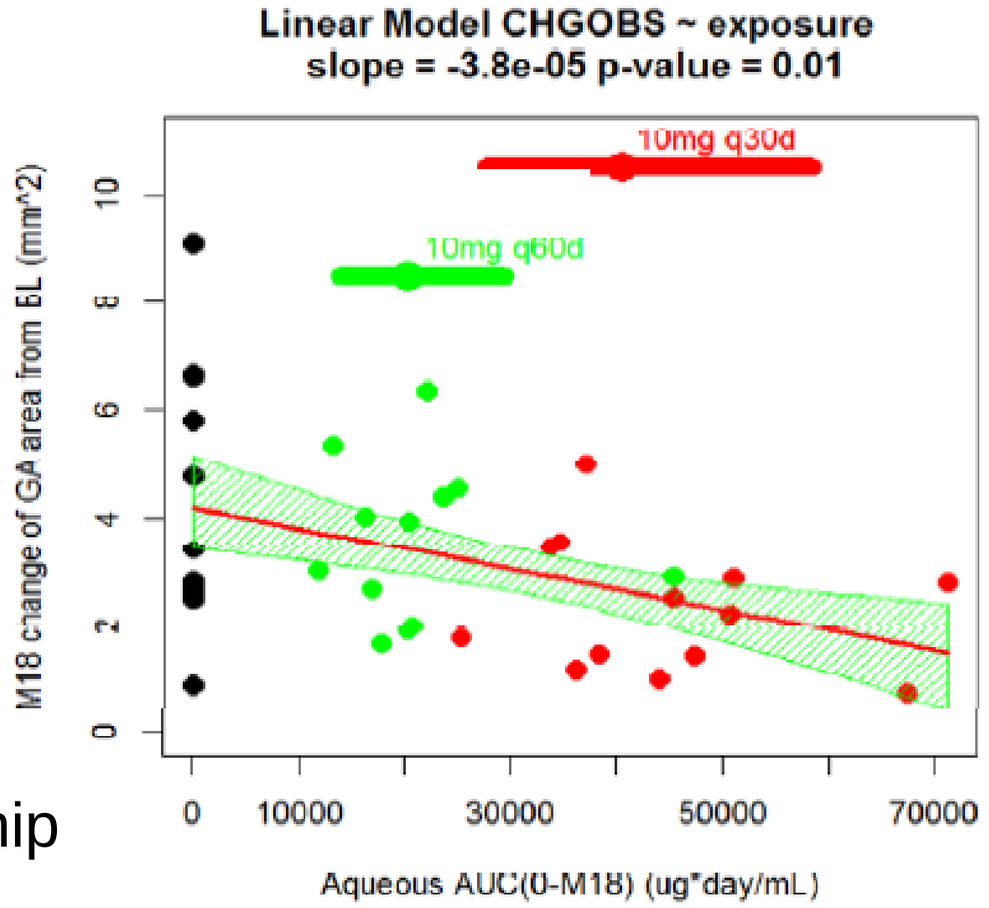
CARDIOVASCULAR DISEASE[15]

RACE – MORE COMMON AMONG CAUCASIANS

Lampalizumab: encouraging Phase 2 results…

Table 20 Study CFD4870g: Mean Change from Baseline in Geographic Atrophy Area at Month 18 (Study Eye): Modified Intent-to-Treat Patients (LOCF Method)

Geographic Atrophy Area at Month 18 (mm^2)	Sham Pooled	Lampalizumab Monthly
Mean change from baseline as assessed by FAF		
n	40	42
Unadjusted mean (SD)	2.872 (2.005)	2.209 (1.309)
LS mean [a]	2.921	2.326
Difference in LS means (vs. sham pooled) [a]		−0.595
80% CI for difference in LS means [a]		(−1.081, −0.109)
p-value (vs. sham pooled) [a]		0.1170
Reduction rate based on LS means [b]		20.4%



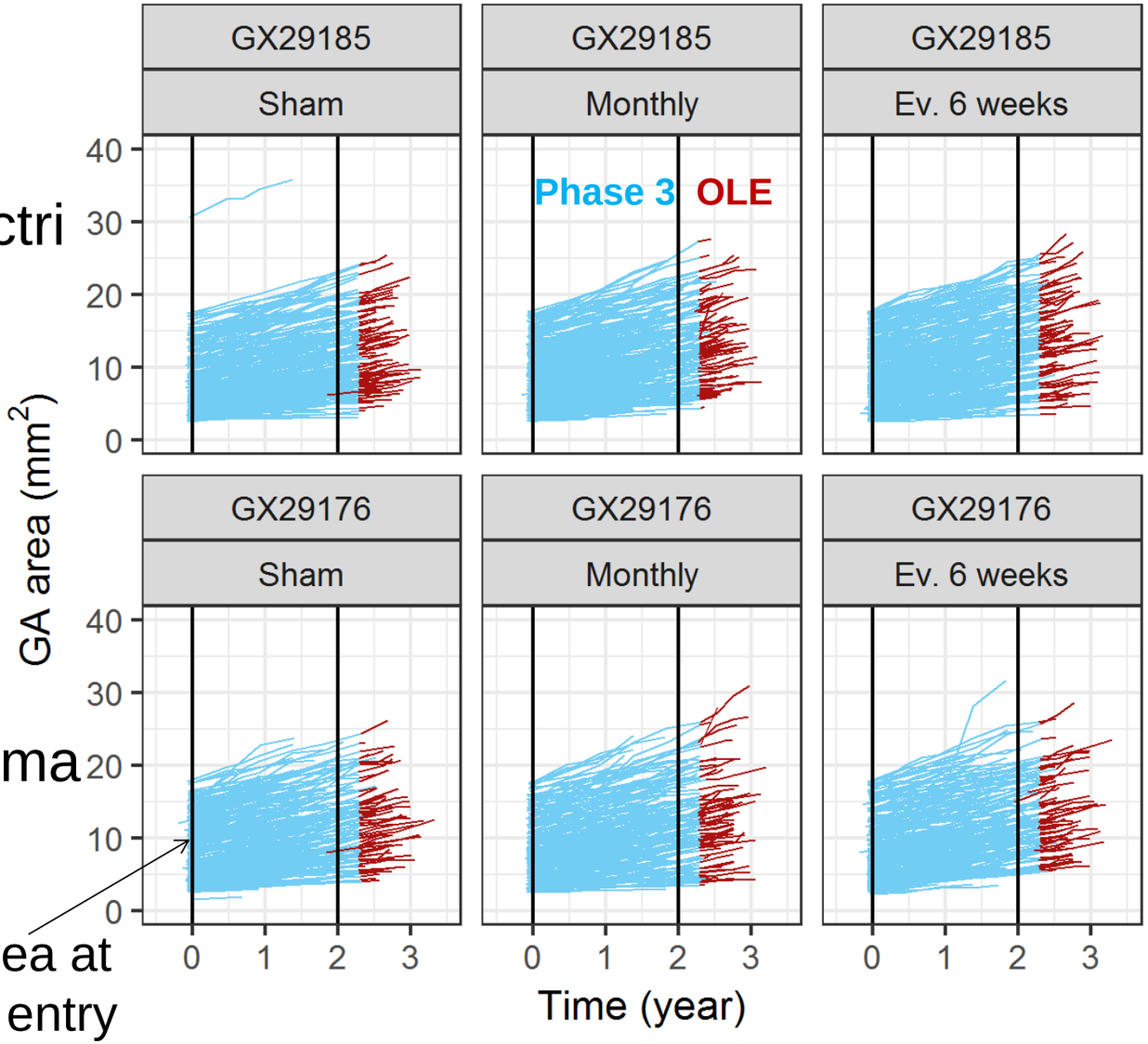
Exposure-Response relationship in serum and aqueous humor

Genentech Clinical PKPD

… but 2 negative Phase 3 trials, let's value the data

Spectri

Chroma



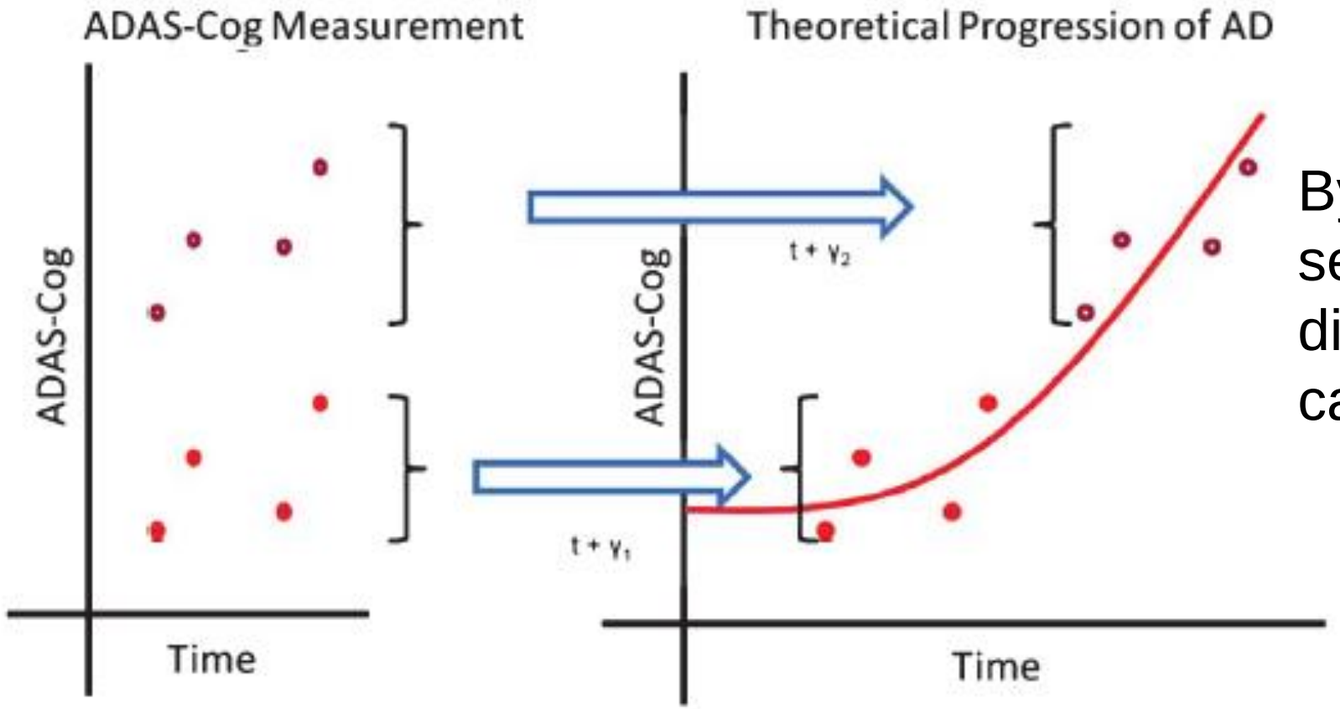
GA area at study entry

- Same pattern across studies and treatment arms, no lampalizumab effect, a disease progression model can be developed on all data
- Objective: disease progression model to SUPPORT DRUG DEVELOPMENT
  - Characterize disease trajectory
  - Identify factors influencing disease progression
- Spectri data used for model development: 970 patients, 6755 GA areas
- Chroma used for external validation and model evaluation: 901 patients

Genentech Clinical PKPD

Modeling approach inspired from Alzheimer's disease

Patients start at a different baseline because they are not at the same disease stage



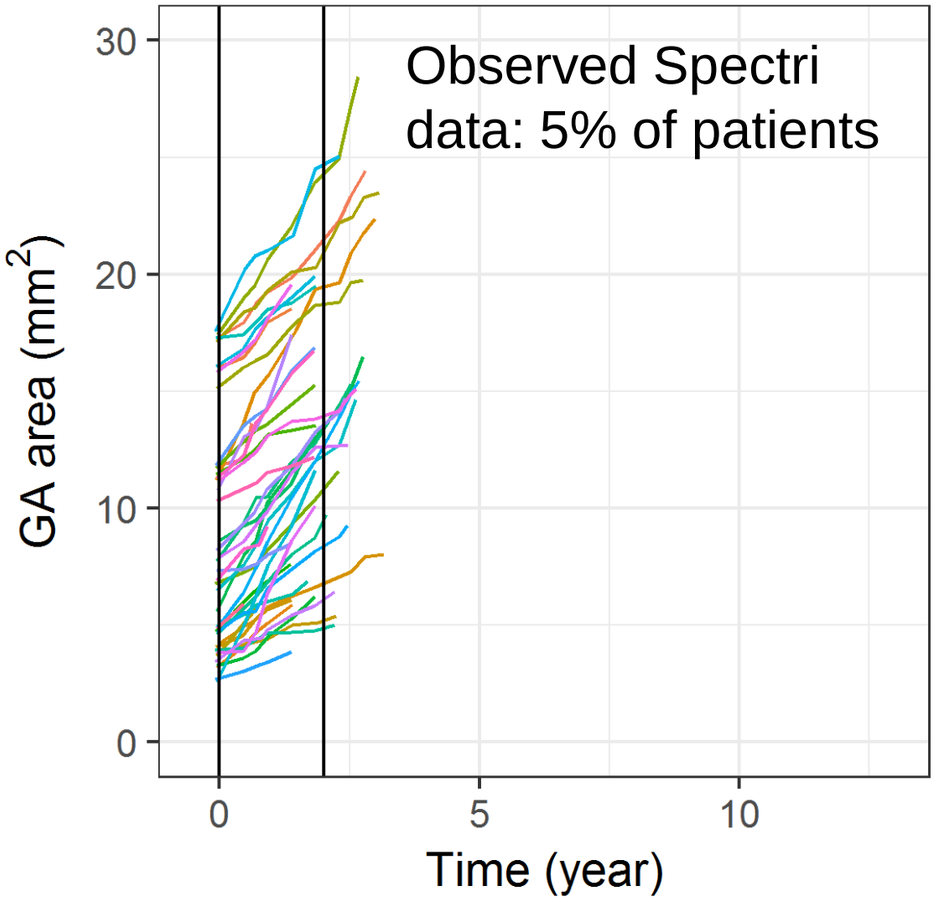
Variation in measurements per time point are due to different stages of disease progression

Rather than assuming that each measurement reflects the same underlying time point, we calculate a time shift (γ) that best fits the data to a theoretical curve of disease progression

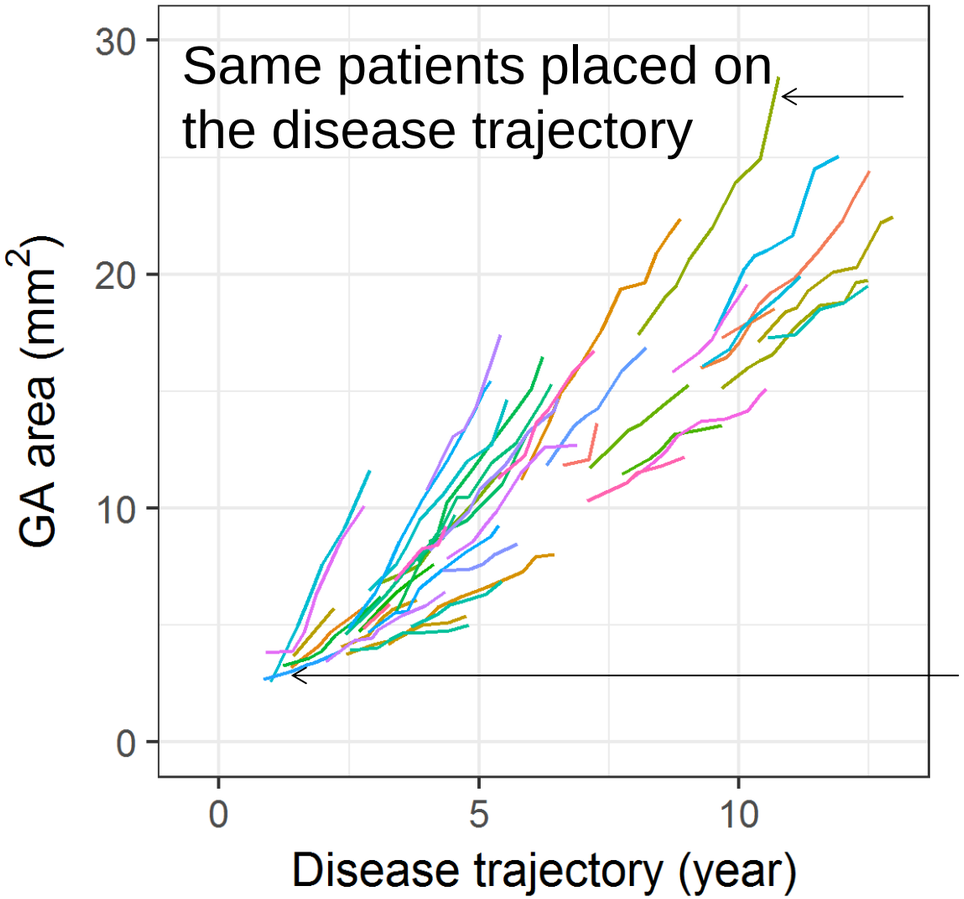
By combining both sets of data, the disease trajectory can be reconstructed

Yang E et al. Journal of Alzheimer's Disease. 26 (2011), 745-753

Application to GA, the “EyeZheimer disease”



Clinical trial time scale



Disease trajectory time scale

Disease onset time estimated to occur 9 years before study entry

Disease onset time estimated to occur 2 years before study entry

Structural model

GA area change (mm^2/y)

$$\frac{dGA}{dt} = (SLOPE + GA \times \alpha) \times \left[\frac{t^{30}}{t^{30} + DOT^{30}}\right]$$

Common linear disease progression rate (/y), no variability

Individual 1st order contribution to disease progression

DOT: Disease Onset Time
GA=0 for t<DOT
Step function to make GA area increasing when t>DOT (y)

Delor I et al. CPT Pharmacometrics Syst Pharmacol. 2013;2, e78; doi:10.1038/psp.2013.54.

Estimated parameters: SLOPE, α, Disease Onset Time (DOT)

GA at study entry as structural covariate

Random effects

- On DOT and α
- Not on SLOPE, SLOPE informed by the whole population therefore individual values cannot be derived

Model developed in NONMEM, Time shift created to estimate DOT, all times shifted to Time+20 (y)

Covariates

GA area at entry: structural covariate

Demographic baseline covariates: age, body weight, sex, race, region

Other baseline covariates: white blood cell count, neutrophils count, glucose, smoking status previous (Yes/No) current (Yes/No)

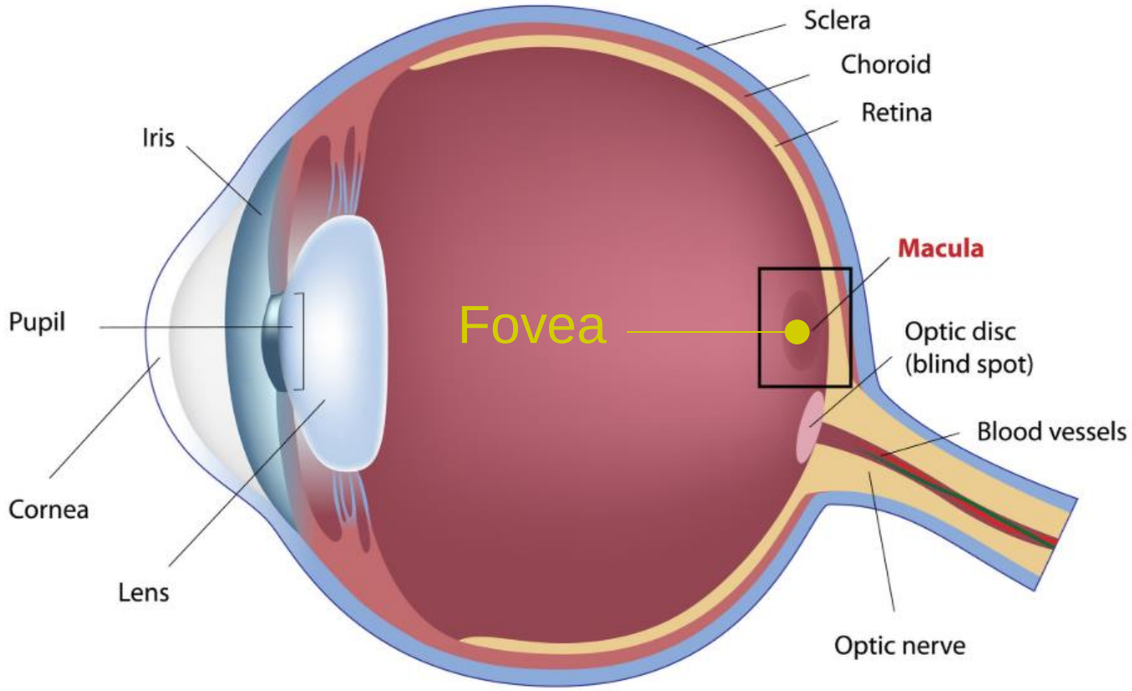
Biomarker status: CFI

Anatomical covariates:

- **Lesion location (Subfoveal/Non subfoveal)**
- Contiguity (Multifocal/Non multifocal)
- Hyperautofluorescence pattern (banded/diffuse)
- Distance to central fovea: not tested because of too many missing values

Forward selection at 0.05 and

backward elimination at 0.01



Covariates

GA area at entry: structural covariate

Demographic baseline covariates: age, body weight, sex, race, region

Other baseline covariates: White blood cell count, neutrophils count, glucose, smoking status previous (Yes/No) current (Yes/No)

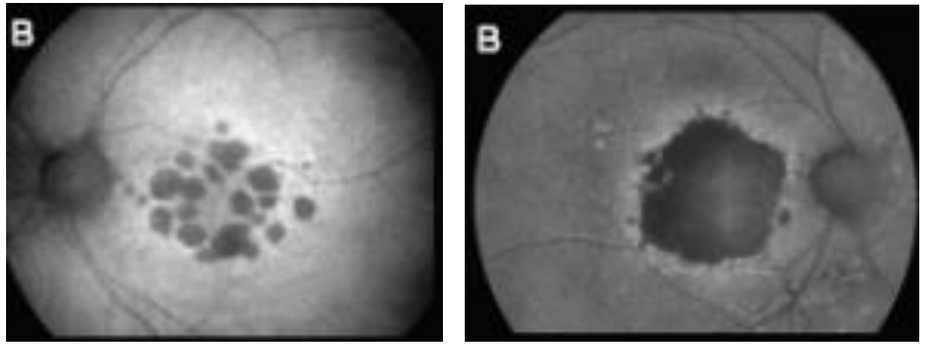
Biomarker status: CFI

Anatomical covariates:

- Lesion location (Subfoveal/Non subfoveal)
- **Contiguity (Multifocal/Non multifocal)**
- Hyperautofluorescence pattern (banded/diffuse)
- Distance to central fovea: not tested because of too many missing values

Forward selection at 0.05 and

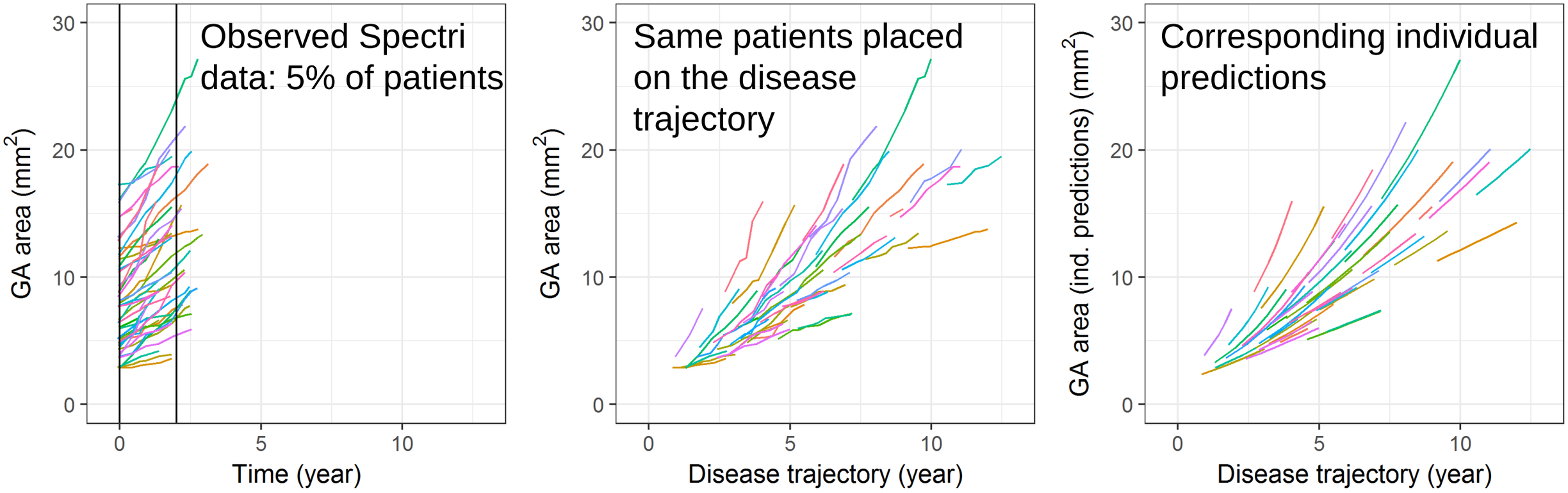
backward elimination at 0.01



Multifocal Non multifocal

Yehoshua Ophthalmic Surg Lasers Imaging Retina. 44 (2013), 127-32.

Disease trajectory: observed versus predicted



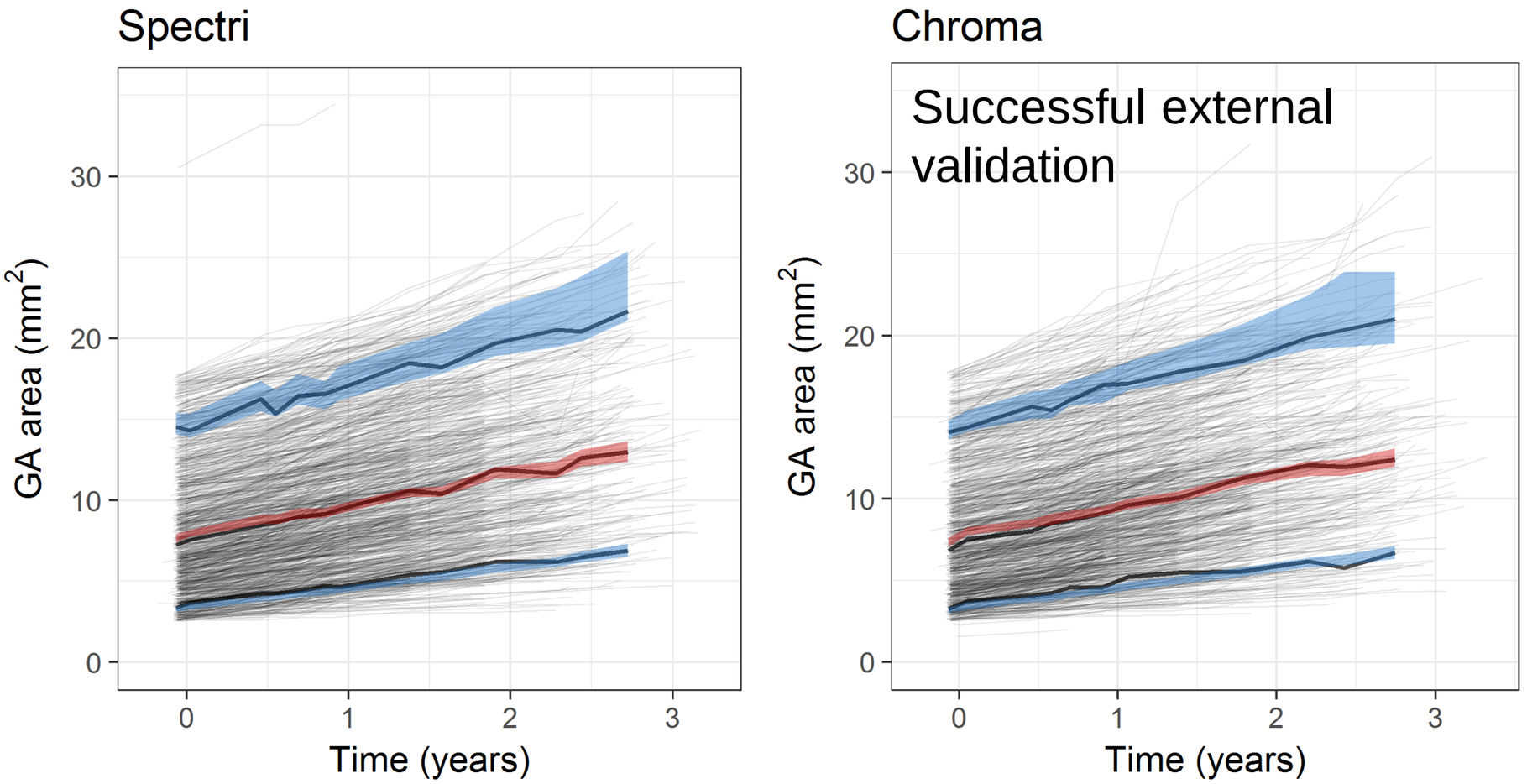
Disease progression seems to be linear with time over the clinical trial duration of 3 years while the overall disease trajectory seems to be non-linear

Genentech Clinical PKPD

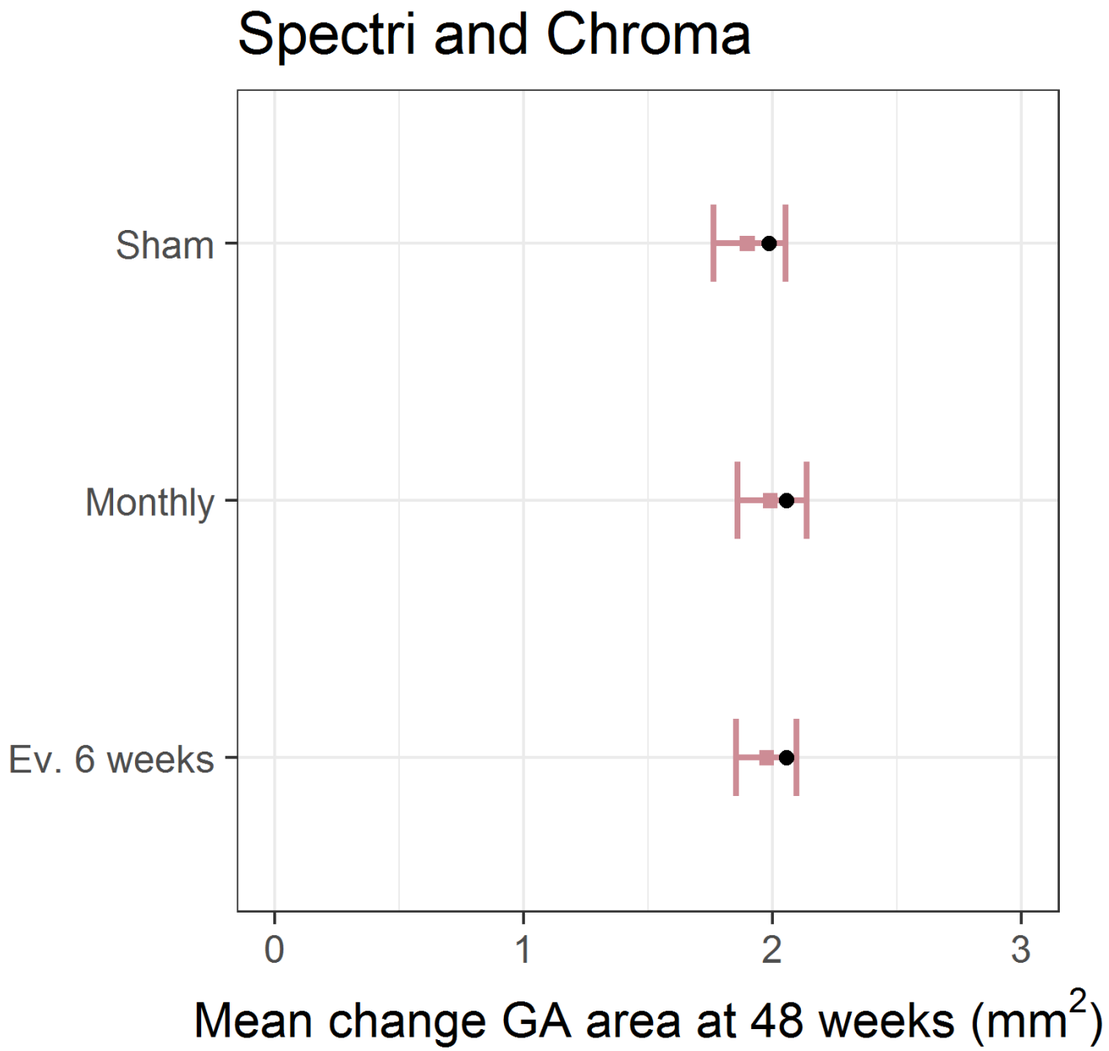
Model qualification: Visual Predictive Checks

Based on 100 replicates

Central tendency and variability very well captured with good precision



Model qualification: Posterior Predictive Checks



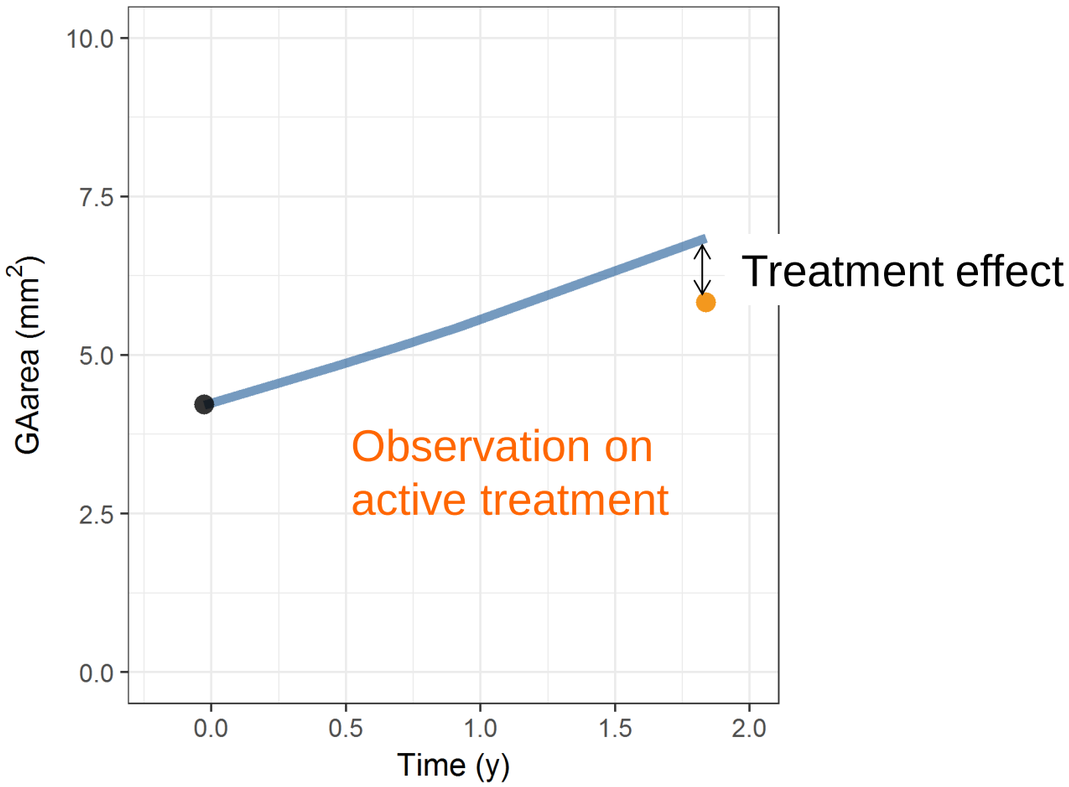
90% prediction interval

- Observed value from Holz F et al. JAMA Ophthalmol.2018;doi:10.1001/jamaophthalmol.2018.1544

The model well predicts 1y mean change from baseline

- With good precision, as individual values range: [0.07;8.65] mm^2

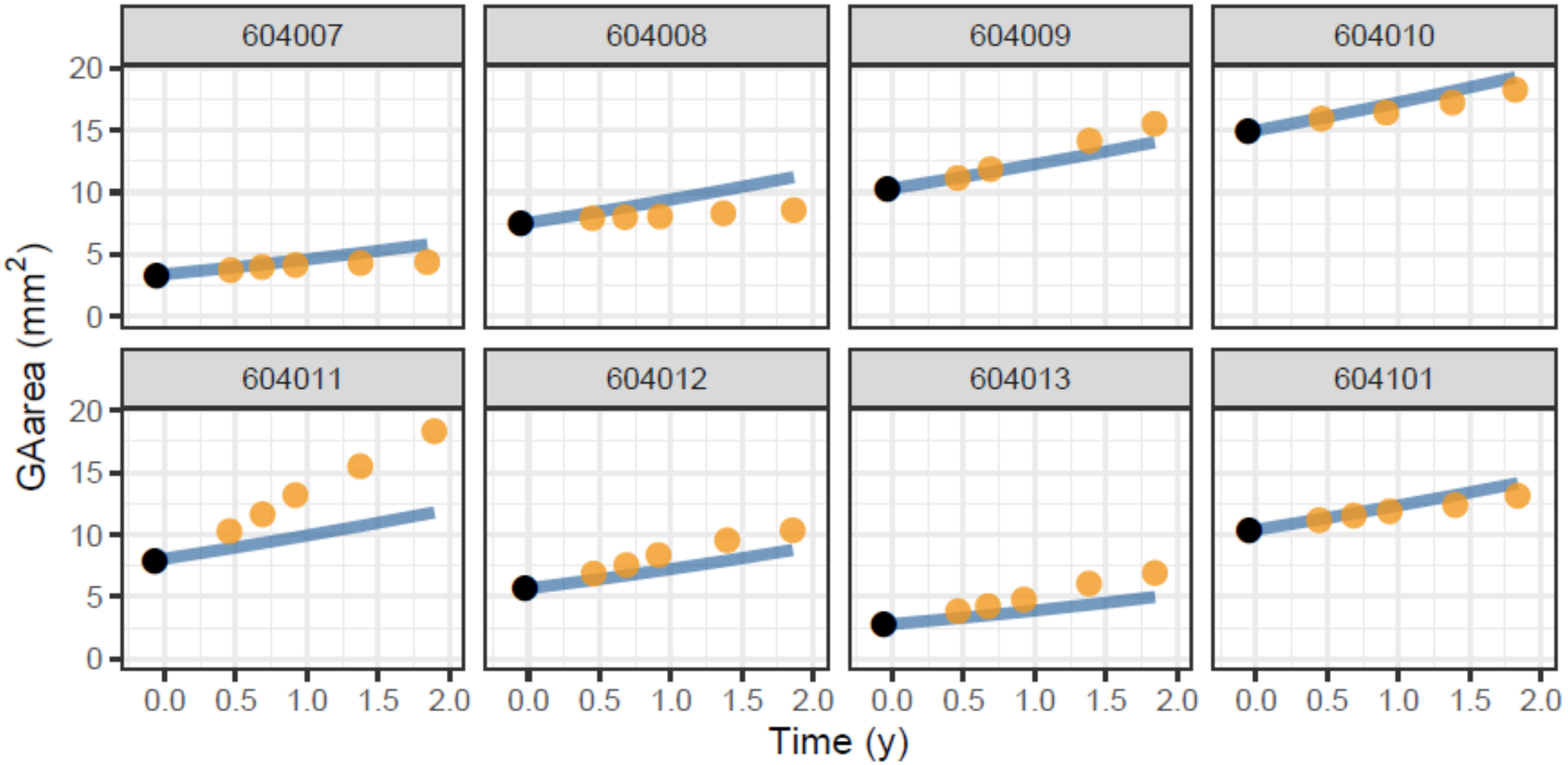
Future use of the model in drug development



The model could be used to predict GA area at 12, 18 or 24 months using historical and baseline individual patient data in absence of treatment

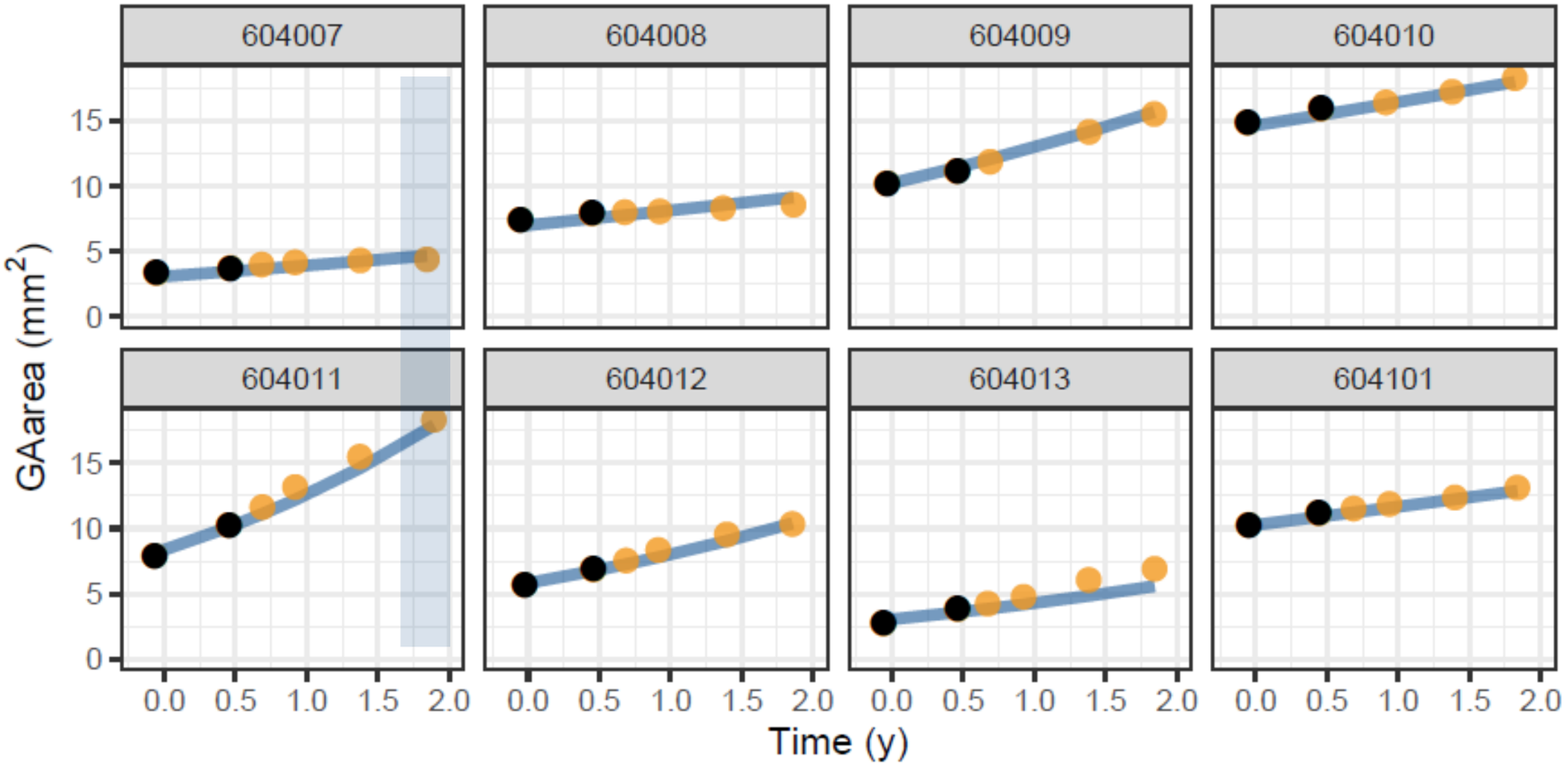
A model-based approach comparing the model-predicted GA area (only due to disease progression) to the corresponding observations (due to disease progression and potential treatment effect) can be an alternative way of assessing treatment effect: a systematic over-prediction in most subjects would suggest a treatment effect

Let’s test the approach on Chroma data



The model predicts fairly well disease progression when informed by only one value, but it is not perfect

Much better with 2 values to inform disease progression



More accurate predictions with two values to inform the model

Hence the importance of collecting historical patient data or perform a run-in period prior to treatment start

Observed mean change from baseline at 2 years: 3.90 [3.69;4.11], SD = 0.11 mm^2

Predicted mean change from baseline at 2 years: 3.85 [3.64;4.05], SD = 0.10 mm^2

Genentech Clinical PKPD

Final Remarks

Development of a disease progression model for geographic atrophy

- The model was developed on one Phase 3 study (and corresponding Open Label Extension) and validated on another Phase 3 study (and corresponding OLE)
- It well characterized the GA area trajectory over time
- Faster progression in patients with GA area at study entry ≥ 6 mm^2, multifocal lesions and non-subfoveal lesions
- It well predicted the primary efficacy endpoint: change from baseline in GA area
- Potential next steps: imaging outputs as additional predictors of disease progression

The model can be used to predict GA disease progression in absence of active treatment to be compared to upcoming observed values from new drug candidate and assess treatment effect

- Importance of collecting 2 GA areas prior to treatment start: run-in period or historical patient data

Acknowledgments

Modeling & Simulation

Jin Jin
Angelica Quartino
Shweta Vadhavkar
Mathilde Marchand (Certara)

Clinical Pharmacology

Rong Deng
Katie Maass
Jason Gow
Logan Brooks
Leslie Dickmann
Amita Joshi

GA Franchise

Ling Ma
Alexandre Fernandez Coimbra
Jamie Taylor
Neha Anegondi
Qi Yang
Verena Steffen
Michel Friesenhahn
Lee Honigberg
Jian Dai
Jasmine Patil
Vahan Indjeian
Christopher Brittain
Simon Gao
May Chen
Christina Rabe
Dolly Chang
Michael Chang
Justin Elstrott

Investigators

Patients

Michèle Chanu

Genentech
A Member of the Roche Group