Skeletal Maturation and Long Bone Growth Patterns of Patients with Progeria: A Retrospective Study

Appendices

Appendix A

Stylized plots illustrating the parameters used in the bone age and bone length models are shown in Figs. A1-2.

Appendix B

The longitudinal growth patterns of the humerus, radius, ulna, and fibula in patients with Progeria are shown in Figs. B1-4.

Appendix C

The fitted statistical models of the humerus, radius, ulna, and fibula in patients with Progeria are shown in Figs. C1-4.

Appendix D

An example illustrating the utility of tibial length prediction based on mixed modeling is shown in Fig. D1.

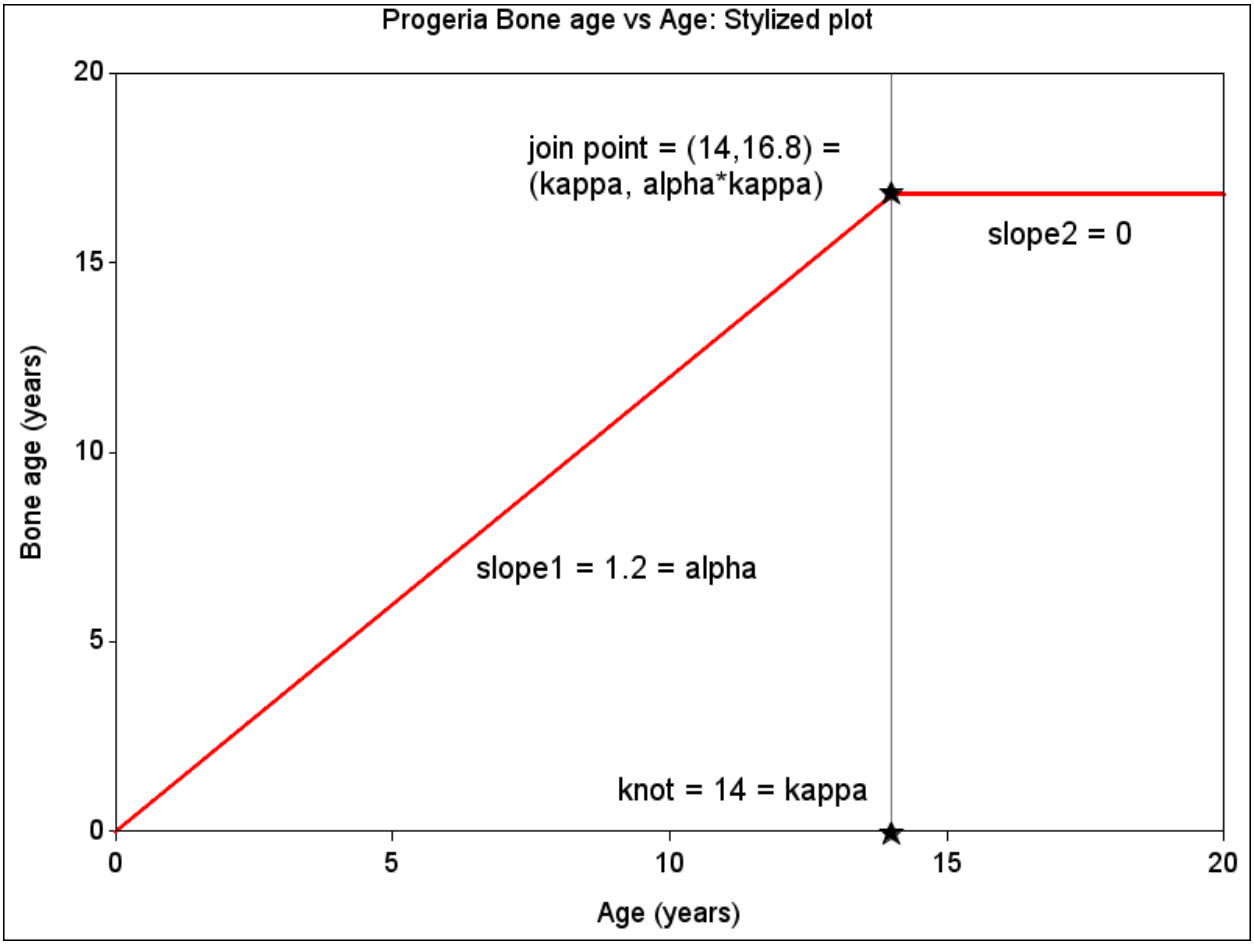

Fig. A1. A stylized plot illustrating parameters in the bone age model for Progeria patients (joined red lines). The stylized version of the bone age model for adolescents is $y = \alpha x$ for $x \leq \kappa$, and $y = \alpha\kappa$ for $x > \kappa$, where y is bone age, x is patient age, κ = 14 is the age of maturity, and α = 1.2 is the rate of maturation per year prior to maturity. Thus the model increases between x = 0 and x = 14 from y = 0 to $y = \alpha\kappa$ = (1.2)(14) = 16.8 (first red line), and is horizontal thereafter (second red line). The single equation that produces both lines is $y = \alpha x - \alpha Max(0, x - \kappa)$.

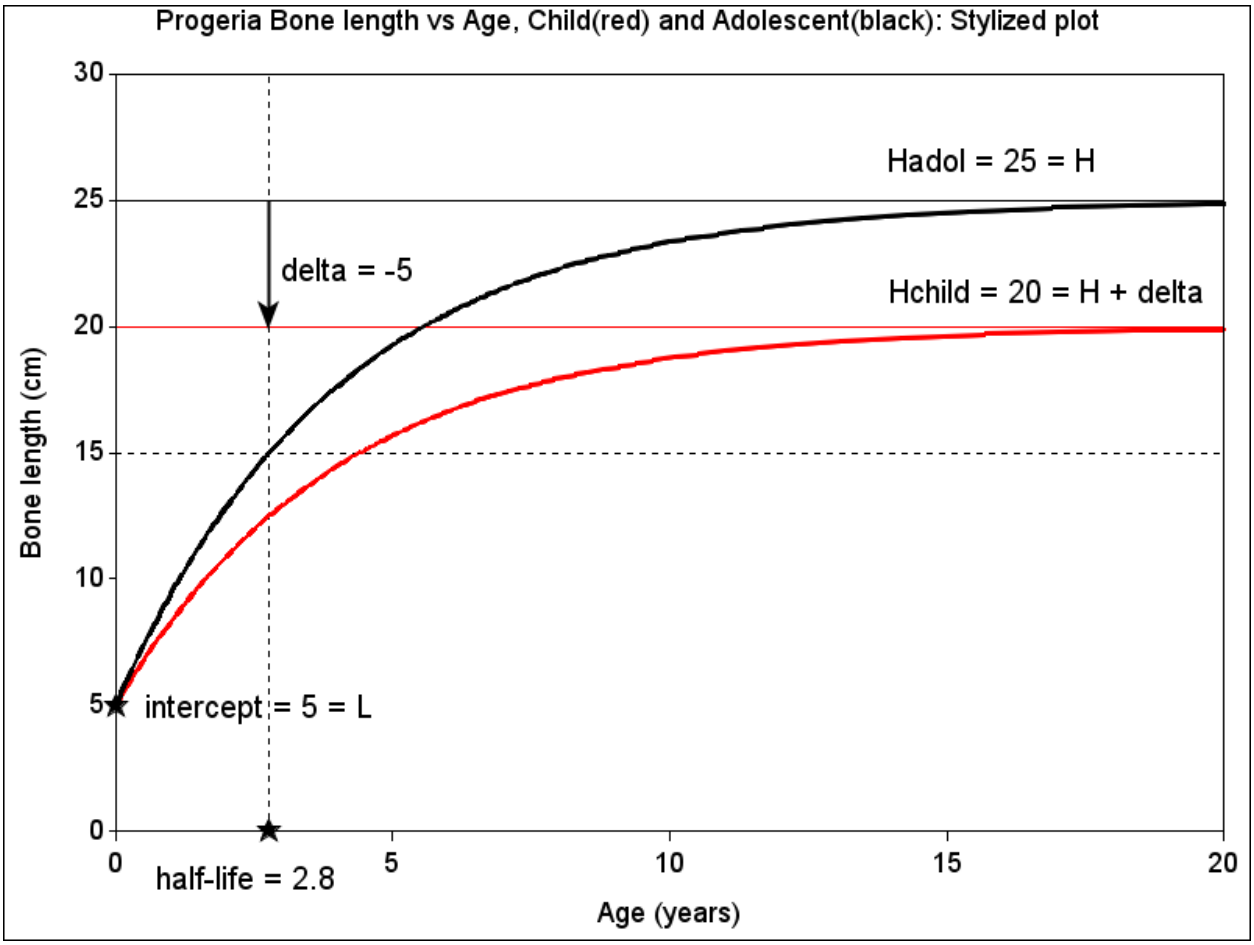

Fig. A2. A stylized plot illustrating parameters in the bone length model for adolescent (black curve) and childhood (red curve) Progeria patients. The stylized version of the bone length model for adolescents is $y = L + (H - L)(1 - \exp(-\beta x))$, where y is length, x is age, $L = 5$ is the intercept (length at birth), $H = 25$ is the asymptote (eventual bone length), and β = 0.25 determines the growth rate. The half-life, the time taken to grow from $L = 5$ to $\frac{(L+H)}{2}$ = 15, is $\frac{\log(2)}{\beta} = 2.8$ years. The model for children shares all parameters except for the asymptote, which is $(H + \delta)$ = (25 – 5) = 20, and thus $y = L + ((H + \delta) - L)(1 - \exp(-\beta x))$. The single equation that produces both curves is $y = L + ((H + \delta M) - L)(1 - \exp(-\beta x))$, where M = 0 for adolescents and M = 1 for children.

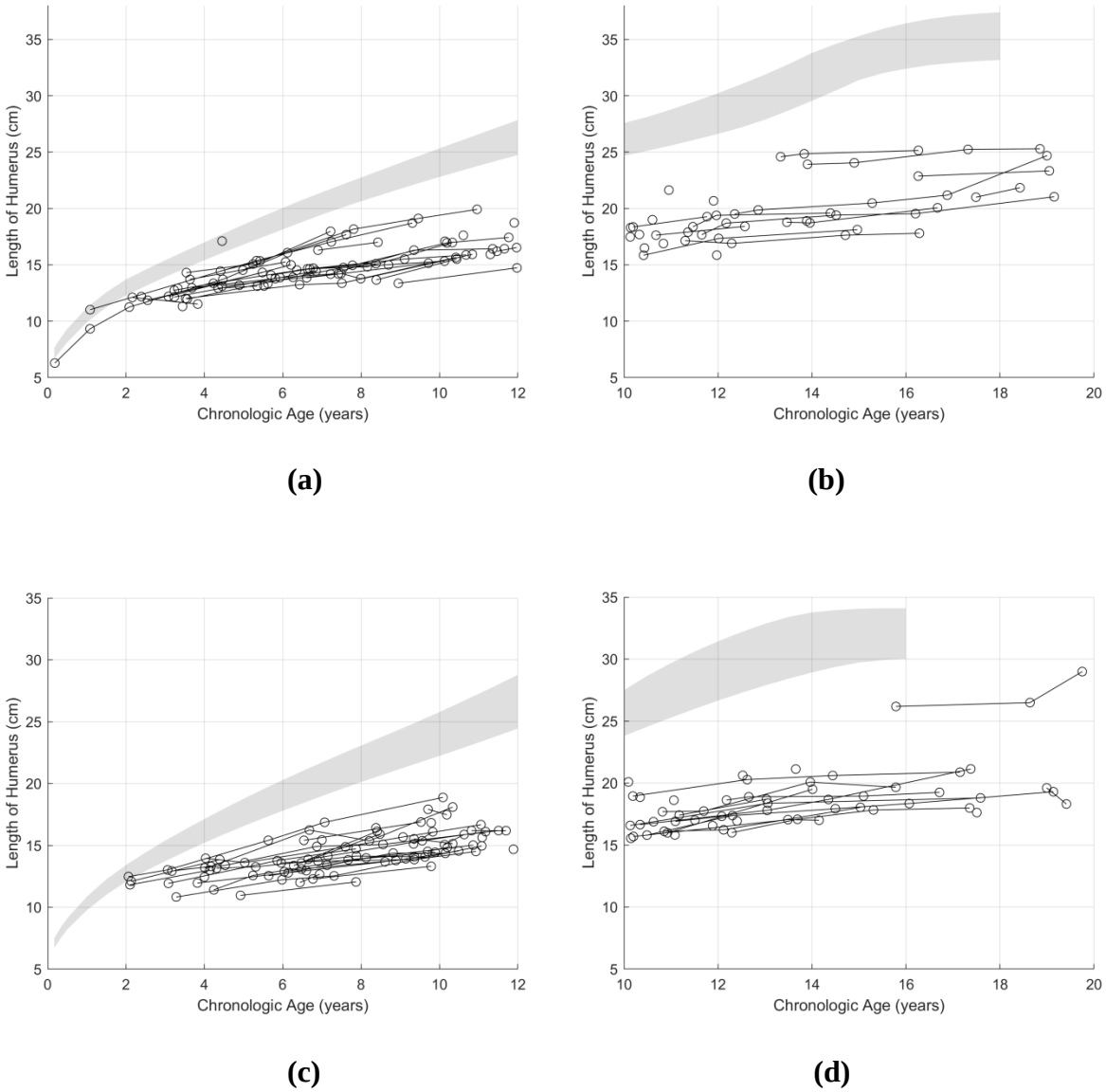

Fig. B1 Longitudinal growth patterns of the ***humerus*** in patients with Progeria. The humerus growth curves of 38 boys ≤12 years old (a), 23 boys ≥10 years old (b), 35 girls ≤12 years old (c), and 25 girls ≥10 years old (d) were plotted in comparison to their respective reference growth standards of Maresh [15]. The population variance, shown in gray, denotes the 10-90% range of normal.

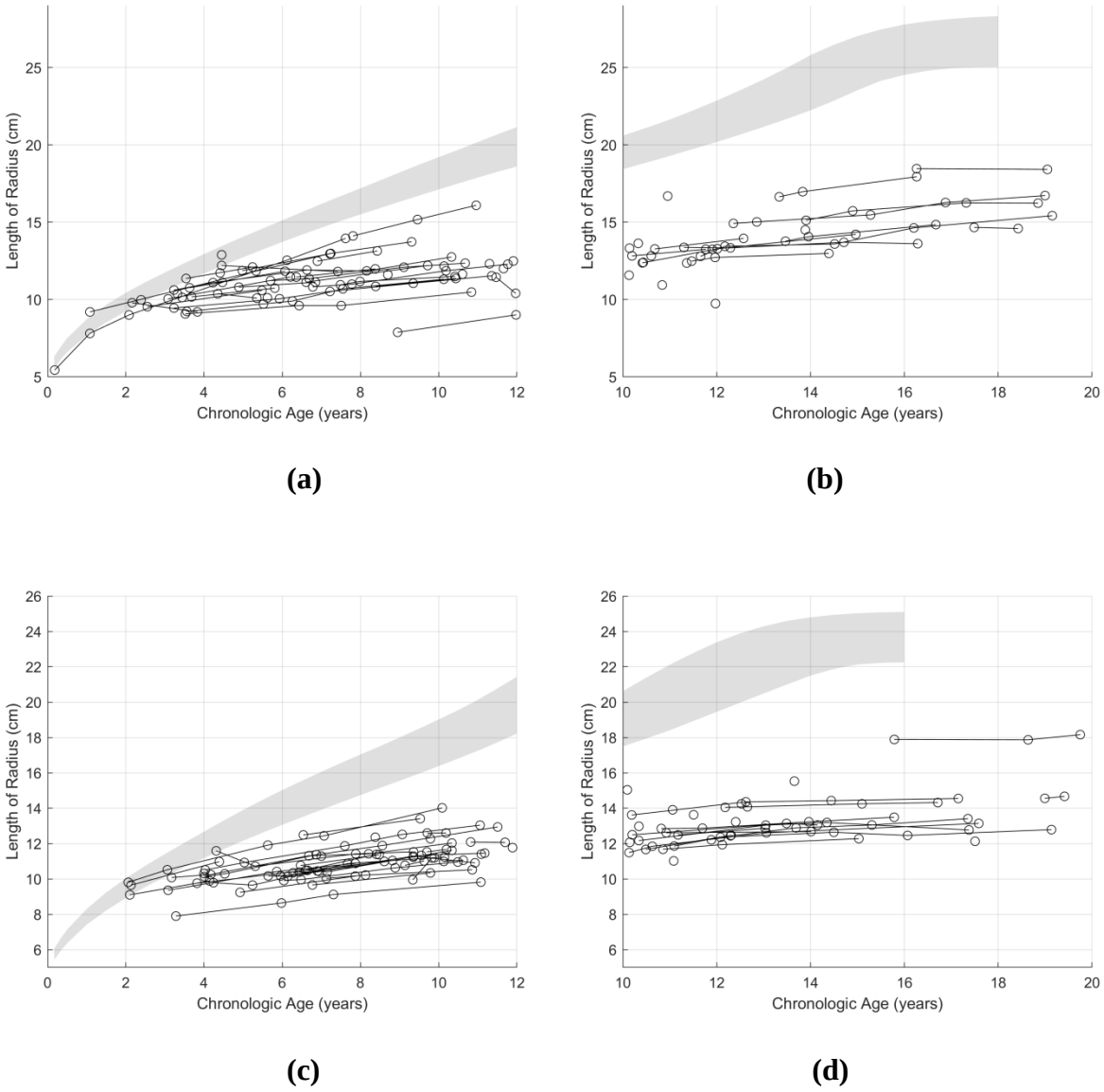

Fig. B2 Longitudinal growth patterns of the ***radius*** in patients with Progeria. The radius growth curves of 38 boys ≤12 years old (a), 23 boys ≥10 years old (b), 35 girls ≤12 years old (c), and 25 girls ≥10 years old (d) were plotted in comparison to their respective reference growth standards of Maresh [15]. The population variance, shown in gray, denotes the 10-90% range of normal.

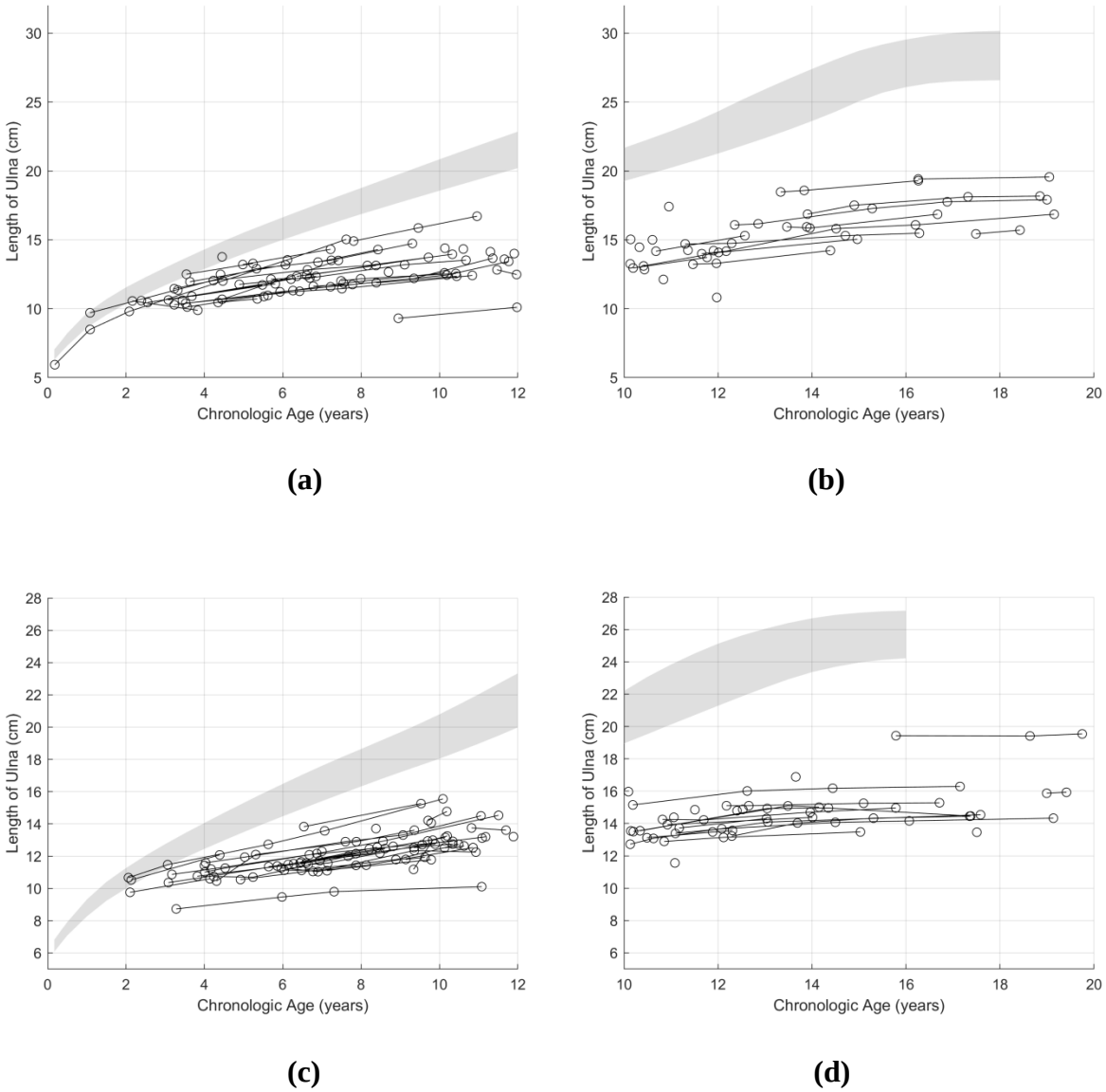

Fig. B3 Longitudinal growth patterns of the ***ulna*** in patients with Progeria. The ulna growth curves of 38 boys ≤12 years old (a), 23 boys ≥10 years old (b), 35 girls ≤12 years old (c), and 25 girls ≥10 years old (d) were plotted in comparison to their respective reference growth standards of Maresh [15]. The population variance, shown in gray, denotes the 10-90% range of normal.

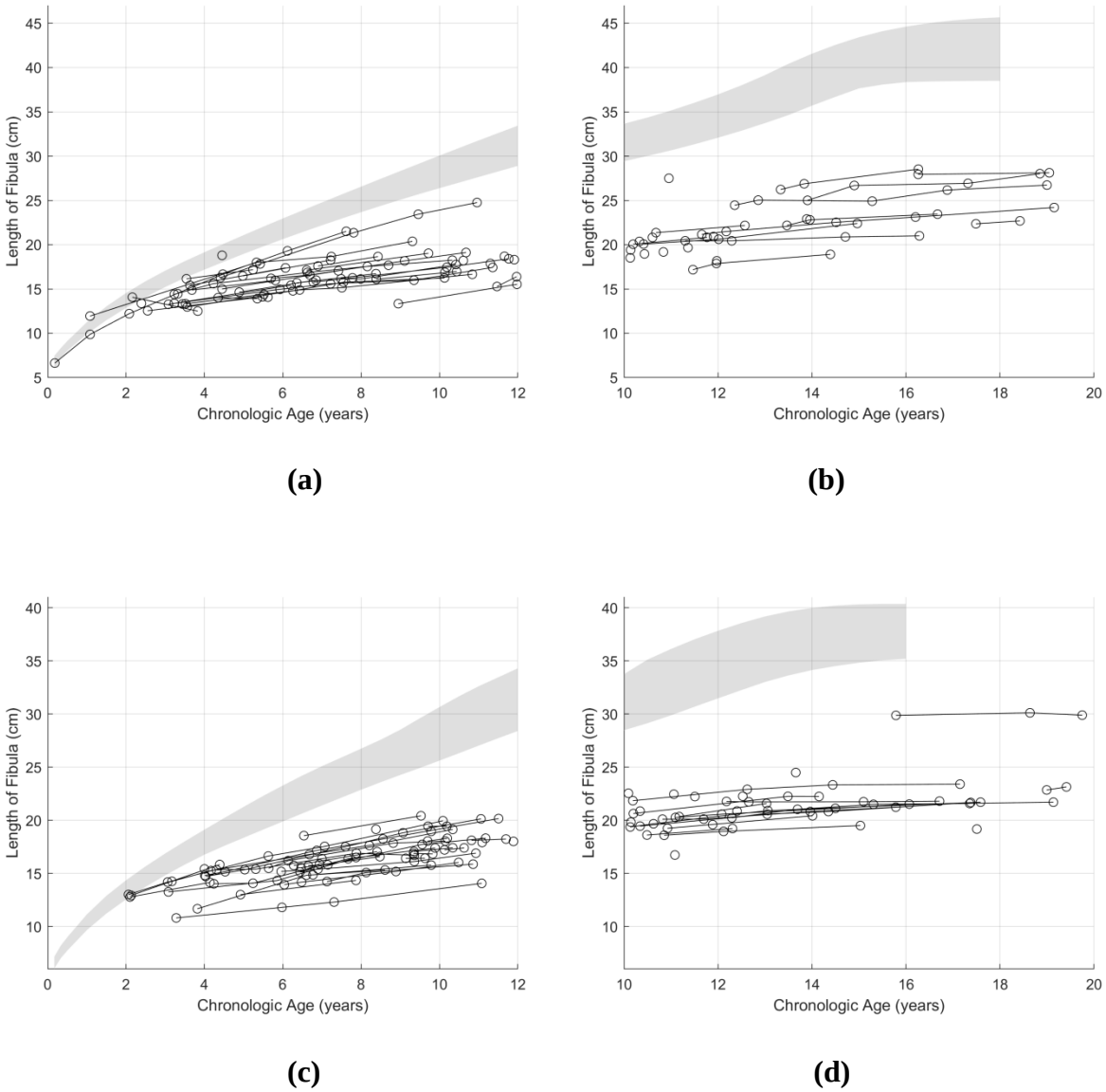

Fig. B4 Longitudinal growth patterns of the ***fibula*** in patients with Progeria. The fibula growth curves of 38 boys ≤12 years old (a), 23 boys ≥10 years old (b), 35 girls ≤12 years old (c), and 25 girls ≥10 years old (d) were plotted in comparison to their respective reference growth standards of Maresh [15]. The population variance, shown in gray, denotes the 10-90% range of normal.

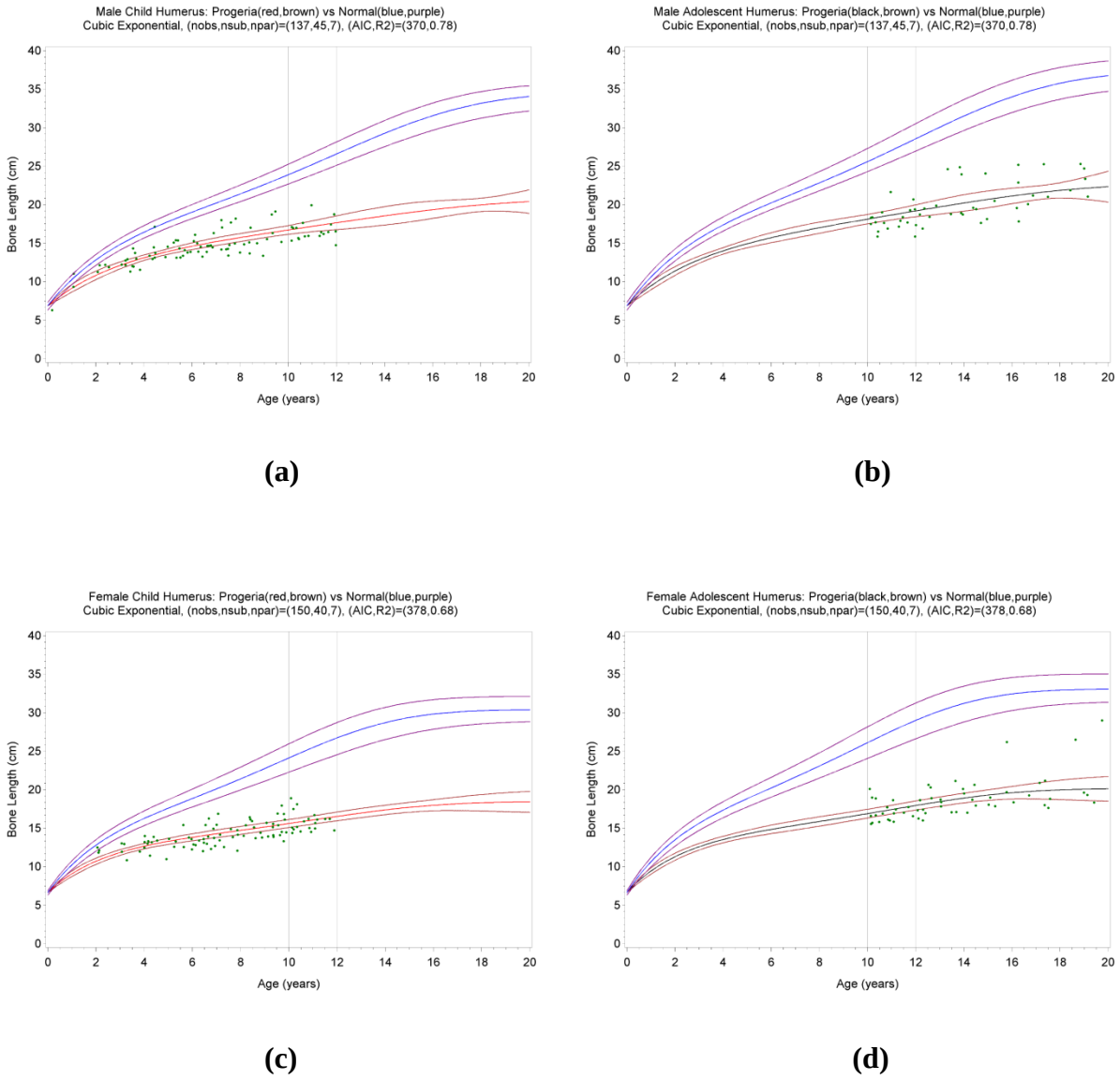

Fig. C1 Fitted statistical models of the ***humerus*** in patients with Progeria. The models for 38 boys ≤12 years old (a), 23 boys ≥10 years old (b), 35 girls ≤12 years old (c), and 25 girls ≥10 years old (d) were plotted in comparison to the normal median (blue line) and range (purple lines). Measurement data are shown as green dots. In (a) and (b), the Progeria model and its 95% confidence intervals were shown as red and brown lines, respectively. In (c) and (d), the Progeria model and its 95% confidence intervals were shown as black and brown lines, respectively.

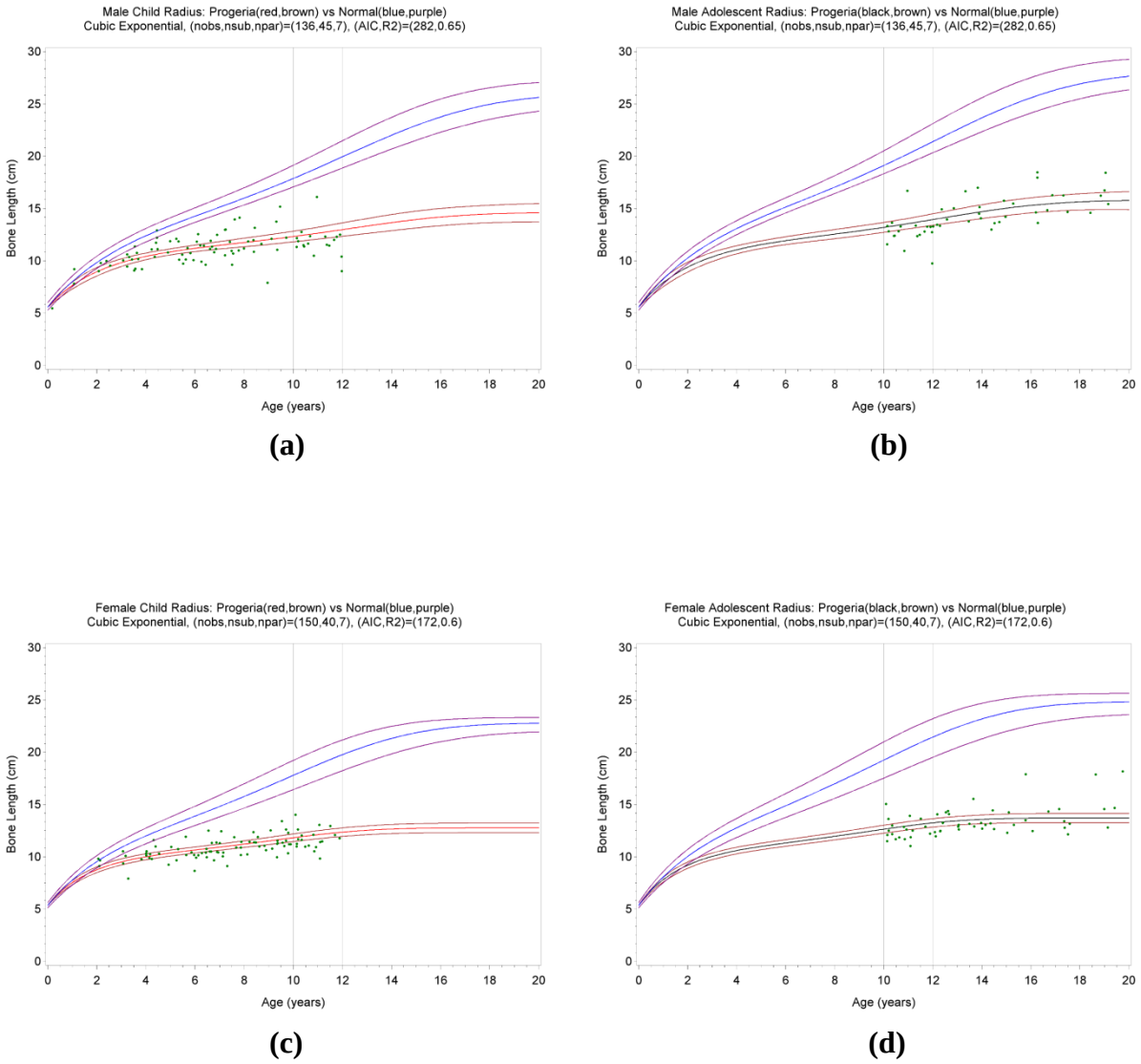

Fig. C2 Fitted statistical models of the ***radius*** in patients with Progeria. The models for 38 boys ≤12 years old (a), 23 boys ≥10 years old (b), 35 girls ≤12 years old (c), and 25 girls ≥10 years old (d) were plotted in comparison to the normal median (blue line) and range (purple lines). Measurement data are shown as green dots. In (a) and (b), the Progeria model and its 95% confidence intervals were shown as red and brown lines, respectively. In (c) and (d), the Progeria model and its 95% confidence intervals were shown as black and brown lines, respectively.

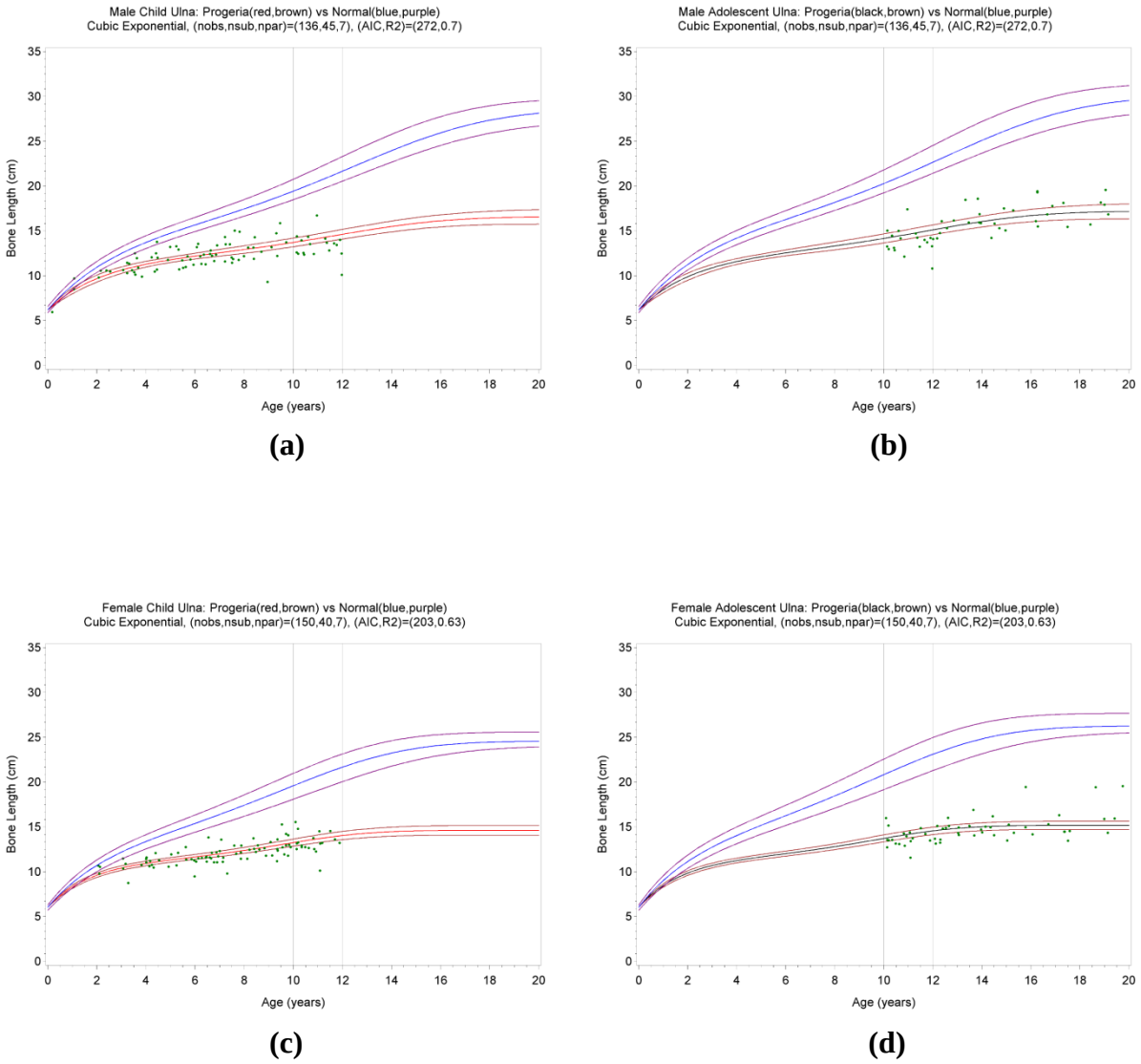

Fig. C3 Fitted statistical models of the ***ulna*** in patients with Progeria. The models for 38 boys ≤12 years old (a), 23 boys ≥10 years old (b), 35 girls ≤12 years old (c), and 25 girls ≥10 years old (d) were plotted in comparison to the normal median (blue line) and range (purple lines). Measurement data are shown as green dots. In (a) and (b), the Progeria model and its 95% confidence intervals were shown as red and brown lines, respectively. In (c) and (d), the Progeria model and its 95% confidence intervals were shown as black and brown lines, respectively.

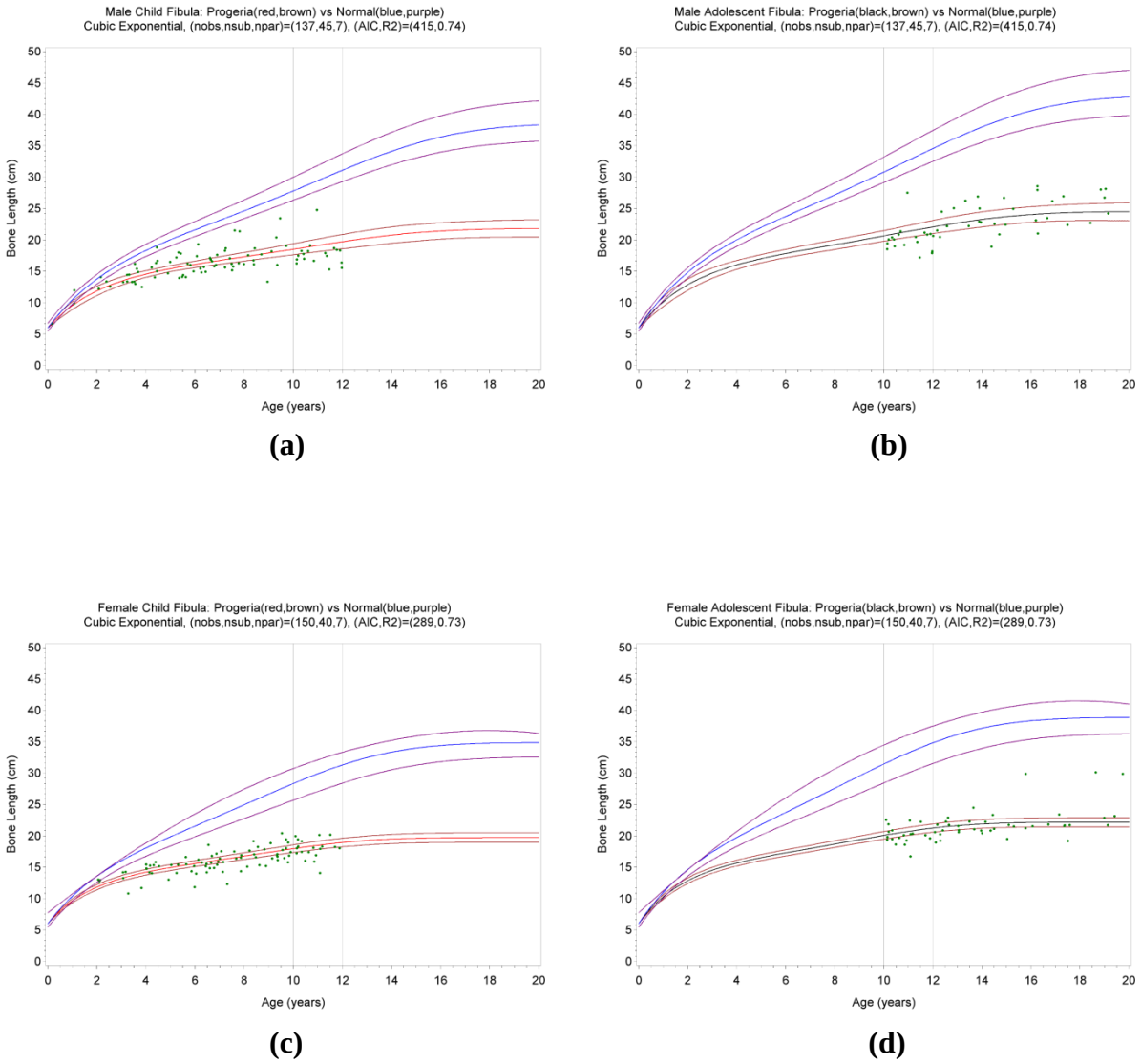

Fig. C4 Fitted statistical models of the ***fibula*** in patients with Progeria. The models for 38 boys ≤12 years old (a), 23 boys ≥10 years old (b), 35 girls ≤12 years old (c), and 25 girls ≥10 years old (d) were plotted in comparison to the normal median (blue line) and range (purple lines). Measurement data are shown as green dots. In (a) and (b), the Progeria model and its 95% confidence intervals were shown as red and brown lines, respectively. In (c) and (d), the Progeria model and its 95% confidence intervals were shown as black and brown lines, respectively.

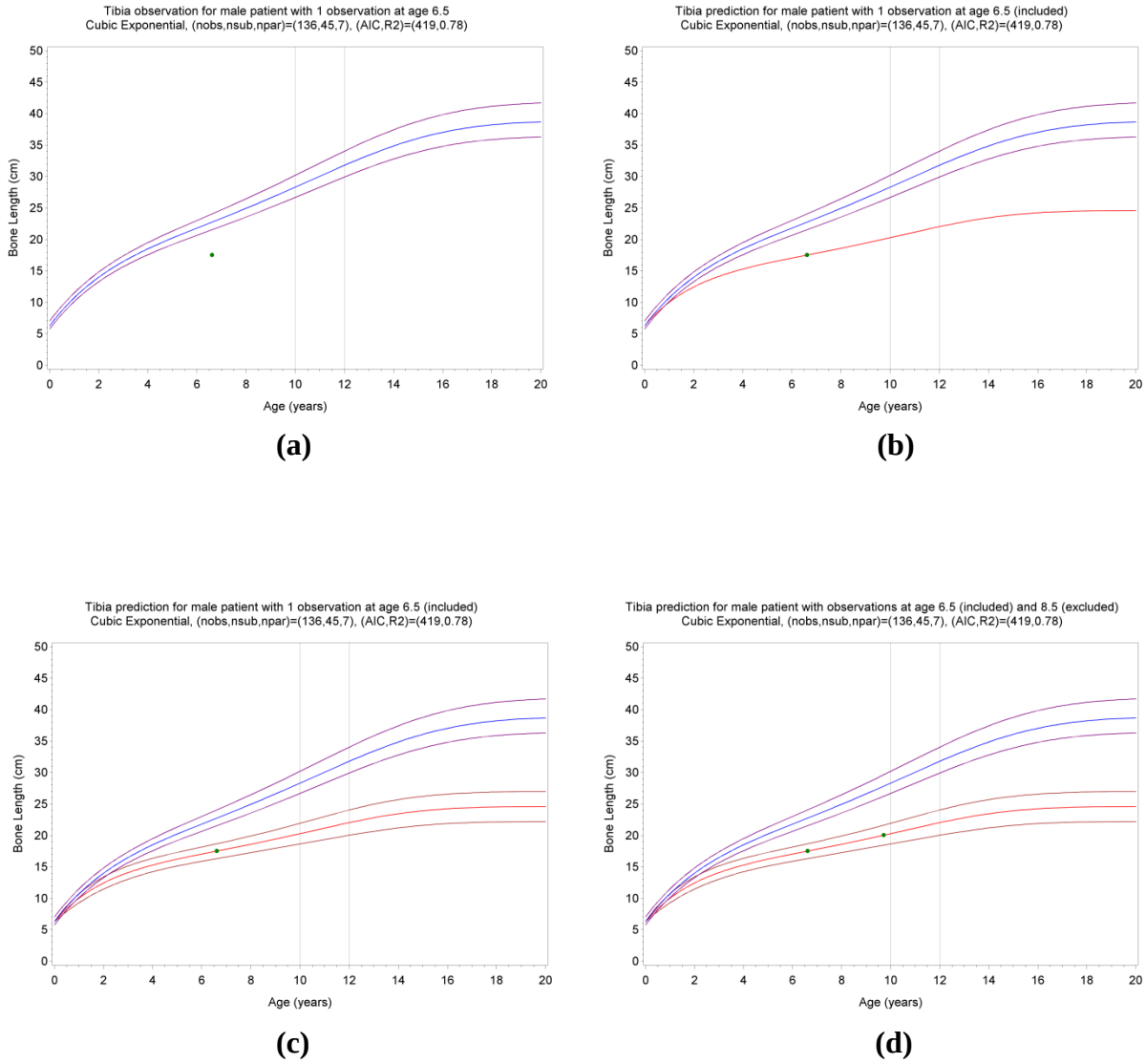

Fig. D1 An example illustrating the utility of tibial length prediction based on mixed modeling. The tibial length of a 6.5 year-old boy with Progeria (green dot) was plotted against his chronologic age (a). The normal median (blue line) and range (purple lines) were plotted in the background for reference. Based on this single tibial length, our mixed statistical model (using only the first observation of this particular subject, along with data from all other subjects) generated a prediction of this child's tibial length over time extending to adulthood (red line) (b). A 95% confidence interval of this prediction (brown lines) was plotted to show the range of uncertainty associated with this prediction (c). At the 2-year follow up appointment, this child's tibial length was measured and plotted against its chronologic age of 8.5 years (second green dot) (d). Note the accuracy of the prediction (red line) when compared to the actual measurement (second green dot).