Reconstructing Granular Onset Age Distributions from Summary Statistics: A Rare Disease Use Case

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Introduction

In rare disease research, we often face a frustrating gap: while age of onset is a critical input for epidemiological models, health economics, and clinical trial design, individual-level data are rarely available. Instead, published studies typically report only summary statistics—a mean here, a median and interquartile range there—leaving modelers with incomplete foundations for age-specific analysis.

This limitation is more than a data inconvenience; it directly impacts the quality of disease burden estimation and market access models that guide resource allocation and patient care.

To address this challenge, we developed a simulation-based framework that reconstructs full onset age distributions from minimal inputs. By fitting plausible parametric distributions to reported quantiles, we can simulate granular age-at-onset profiles—including age-band–specific incidence proportions with uncertainty intervals.

This Python notebook demonstrates the approach using a real-world example: anti-GABABR encephalitis, a rare autoimmune encephalitis subtype. In this case, only quantile data were reported, and individual patient data were inaccessible. Yet through distribution modeling, we recreated actionable onset distributions for downstream use.

Our method draws inspiration from a technique introduced by Dr. Rick Wicklin in his SAS blog post, where he showed how to fit parametric models to summary statistics using quantile-matching optimization. We've adapted and extended it for use in Python and applied it specifically to the context of rare disease epidemiology.

What You'll Learn:
• How to derive age-band–specific disease burden estimates from published quantile data
• A step-by-step modeling workflow tailored to rare diseases
• Reusable, lightweight code that can be customized for other indications

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Whether you're preparing an HTA submission or estimating global incidence for an underdiagnosed condition, this method offers a scalable, transparent solution when raw data aren't an option—but robust modeling still is.

Workflow Overview

The workflow begins with choosing plausible parametric distributions, informed by both clinical understanding of the disease's onset profile and statistical flexibility. In rare diseases like anti-GABABR encephalitis, where access to individual patient data is limited, this method provides a practical path to reconstruct granular onset age distributions from published summary statistics.

Each step is designed to ensure the simulation is both transparent and robust for downstream applications such as disease burden estimation and HTA modeling:

1. Define Modeling Rationale Select plausible distributions (e.g., log-normal, Weibull, generalized gamma) based on the expected shape and skewness of onset age.
2. Fit Candidate Distributions Use reported quantiles (e.g., median, Q1, Q3) to estimate distribution parameters using a quantile-matching optimization approach.
3. Assess Goodness-of-Fit Evaluate candidate fits by comparing model-derived vs. reported quantiles (e.g., sum of squared errors) and inspecting visual fit.
4. Simulate Onset Ages Generate synthetic patient-level onset ages from the best-fitting distribution.
5. Calculate Age-Band Proportions Aggregate simulated data into age bands (e.g., 0–12, 13–17, 18+), enabling downstream epidemiological and economic analysis.
6. Estimate Uncertainty via Bootstrap Use resampling to compute 95% confidence intervals for each age-band proportion.
7. Conduct Sensitivity Analysis Explore robustness of results by varying distribution parameters within plausible bounds and comparing output across scenarios.

Import required library

In [1]:
```
import numpy as np
import pandas as pd
import matplotlib.pyplot as plt
import seaborn as sns
from scipy.stats import lognorm, weibull_min, gamma, genextreme # Importing neces
# from scipy.optimize import minimize # Optimization for parameter fitting
# from scipy.stats import probplot # Probability plot for visual assessment
# from sklearn.metrics import mean_squared_error # Mean Squared Error for goodnes
# from scipy.stats import gaussian_kde # Kernel Density Estimation for smooth CDF
```

Input Data: Published summary statistics for AIE

Example input data is derived from a published observational study by Lamblin et al. (2024), which investigated autoimmune encephalitis patients in France and the Netherlands. The input includes the median, 25th and 75th percentiles (Q1 and Q3), minimum and maximum values, mean, and reported sample size.

The DOI of the publication: 10.1212/NXI.0000000000200229

The detailed values are as follows:

In [2]:
```
median = 66
q1 = 61
q3 = 72
min = 19
max = 88
mean = 67
size = 111
```

In the following distribution simulation, I will use median, q1 and q3 to fit multiple candidate distributions, using quantile matching method to optimize parameters.

Fitting select distributions

Rational of parametric distributions selection

According to the literature on autoimmune encephalitis (AIE) onset age, the distribution is often significantly right-skewed, with a higher concentration of adult patients and fewer pediatric cases. In certain subtypes, the distribution also exhibits substantial kurtosis, deviating markedly from a normal distribution. These clinical patterns suggest that parametric distributions capable of accommodating both skewness and heavy tails are suitable candidates for simulating age distributions in real-world populations.

Including both classic distributions such as log-normal and Weibull, and more flexible ones like generalized gamma, helps capture a wide range of distribution shapes, accounting for variations in skewness and kurtosis—that is, the asymmetry and tail heaviness of the distribution.

Fitting Log-normal distribution

The log-normal distribution assumes that the logarithm of onset age follows a normal distribution.

- Why it's plausible: It naturally models right-skewed data, which is common in diseases that mostly affect adults but may have early-onset outliers.
- Use case: Often used in time-to-event models where values cannot be negative.

Two parameters to fit in log-normal distribution:

- mu: log-scale mean
- sigma: log-scale SD

Quantile matching with optimization

In this approach, we use a quantile-matching method: we fit candidate distributions (e.g., log-normal, gamma, Weibull) by optimizing their parameters such that their theoretical quantiles align with reported values (e.g., Q1 = 8, Median = 10, Q3 = 14). This requires constrained optimization to ensure valid parameter ranges (e.g., positive shape/scale).

Below is an implementation of this method to fit a log-normal distribution.

In [ ]:
```
import numpy as np
from scipy.stats import lognorm
from scipy.optimize import minimize # Optimization for parameter fitting
```

In [12]:
```
# Empirical quantiles
empirical_q = [q1, median, q3]
```

In [20]:
```
# Objective function: Minimize squared differences between model and empirical qu
def objective(params):
    mu, sigma = params
    if sigma <= 0:
        return np.inf
    dist = lognorm(s=sigma, scale=np.exp(mu))
    theo_q = dist.ppf([0.25, 0.5, 0.75])
    return np.sum((np.array(theo_q) - empirical_q)**2)
```

This defines the objective function for optimization:

- Takes parameters mu and sigma as input
- Returns infinity if sigma is non-positive (constraint)
- Calculates theoretical quantiles using the log-normal distribution with given parameters
- Returns the sum of squared differences between theoretical and empirical quantiles (this is what we want to minimize)

In [21]:
```
# Initial guess for mu and sigma
initial_guess = [np.log(median), 0.5]
bounds = [(0, None), (0.01, 5)]
```

This sets up the optimization:

- `initial_guess` : Starting values for mu (log of median) and sigma (0.5)
- `bounds` : Constraints for the parameters - mu ≥ 0, sigma between 0.01 and 5

In [22]:
```
# Optimize
result = minimize(objective, x0=initial_guess, bounds=bounds)
mu_fit, sigma_fit = result.x

print(f'Fitted parameters:\n mu = {mu_fit:.3f}, sigma = {sigma_fit:.3f}')
```

```
Fitted parameters:
 mu = 4.192, sigma = 0.123
```

This performs the actual optimization:

- Uses scipy's `minimize` function to find the best-fitting parameters
- Extracts the fitted parameters from the result
- Prints the optimized mu and sigma values

The overall process implements **quantile matching** - a method where distribution parameters are estimated by minimizing the difference between theoretical quantiles (from the assumed distribution) and empirical quantiles (from the observed data).

This is particularly useful when we only have summary statistics rather than the full dataset.

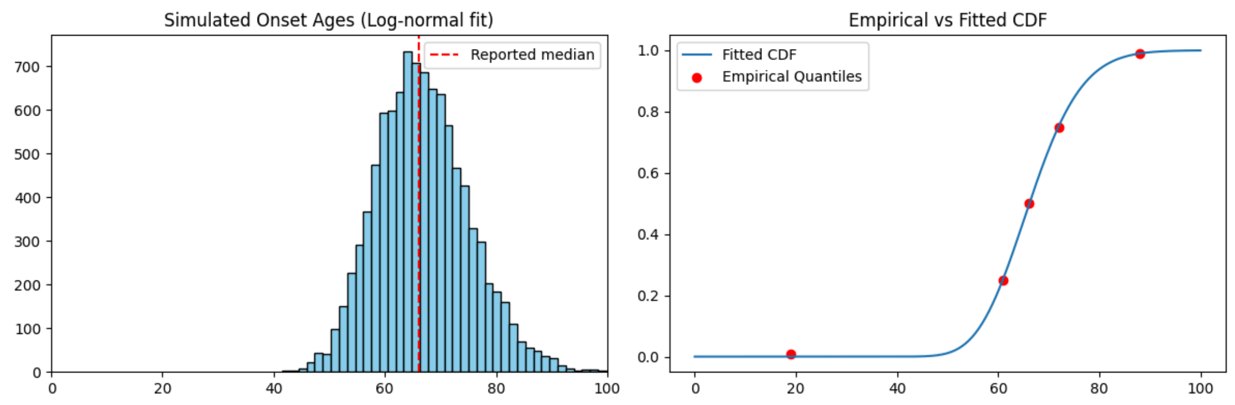
Simulate and visualize fitted distribution

In [24]:
```
import matplotlib.pyplot as plt
```

In [26]:
```
# Generate simulated onset ages
sim_ages = lognorm(s=sigma_fit, scale=np.exp(mu_fit)).rvs(10000)
```

The function `.rvs(10000)` generates 10,000 random variates (samples) from this fitted distribution. The result is stored in `sim_ages`, which contains 10,000 simulated onset ages

In [56]:
```
# Plot histogram + CDF overlay
fig, ax = plt.subplots(1,2, figsize=(12,4))

# Histogram
ax[0].hist(sim_ages, bins=50, color='skyblue', edgecolor='black')
ax[0].axvline(x=median, color='red', linestyle='--', label='Reported median')
ax[0].set_xlim(0, 100)  # Set x-axis range from 0 to 100
ax[0].set_title('Simulated Onset Ages (Log-normal fit)')
ax[0].legend()

# CDF comparison
x = np.linspace(0, 100, 300) # Age range for CDF from 0 to 100
model_cdf = lognorm(s=sigma_fit, scale=np.exp(mu_fit)).cdf(x) # Call cumulative c
ax[1].plot(x, model_cdf, label='Fitted CDF')
ax[1].scatter([min, q1, median, q3, max], [0.01, 0.25, 0.5, 0.75, 0.99], color='r
ax[1].set_title('Empirical vs Fitted CDF')
ax[1].legend()

plt.tight_layout()
plt.show()
```



Left panel shows the log-normal distribution of age at onset for anti-GABABR AIE, with the y-axis indicating patient counts. Right panel displays the cumulative distribution function (CDF) of the log-normal distribution alongside the empirical quantiles.

Fitting Weibull distribution

The Weibull distribution is a versatile survival model that can capture both increasing and decreasing hazard rates, depending on its shape parameter.

- Why it's plausible: It provides flexibility in capturing skewness and hazard patterns, making it suitable for onset age modeling when early or late peaks are expected.
- Use case: Common in clinical and industrial reliability models.

Fit 2-parameter in Weibull distribution:

- c: Shape parameter
- λ: Scale parameter

In [34]:
```
import numpy as np
from scipy.stats import weibull_min
from scipy.optimize import minimize
```

In [40]:
```
# Define quantile matching objective for Weibull
def weibull_objective(params):
    shape, scale = params
    if shape <= 0 or scale <= 0:
        return np.inf
    dist = weibull_min(c=shape, scale=scale)
    theo_q = dist.ppf([0.25, 0.5, 0.75])
    return np.sum((np.array(theo_q) - empirical_q) **2)
```

In [41]:
```
# Initial guess for shape and scale
initial_guess_weibull = [2, 10]
bounds_weibull = [(0.01, None), (0.01, None)]

result_weibull = minimize(weibull_objective, x0=initial_guess_weibull, bounds=bou
shape_fit_weibull, scale_fit_weibull = result_weibull.x

print(f"Fitted Weibull parameters:\n shape = {shape_fit_weibull:.3f}, scale = {sc
```

```
Fitted Weibull parameters:
 shape = 9.460, scale = 69.247
```

Setup and Optimization:

- `initial_guess_weibull = [2, 10]` : Starting values for the optimization
  - Shape parameter (c) = 2
  - Scale parameter (λ) = 10
- `bounds_weibull = [(0.01, None), (0.01, None)]` : Parameter constraints
  - Both shape and scale must be ≥ 0.01 (positive values)
  - No upper bounds (None)

Optimization Process:

- `minimize(weibull_objective, x0=initial_guess_weibull, bounds=bounds_weibull)` : Uses scipy's minimize function to find the best-fitting Weibull parameters
- `weibull_objective` : The objective function defined in the previous cell that minimizes squared differences between theoretical and empirical quantiles
- `result_weibull.x` : Extracts the optimized parameters from the result

Output:

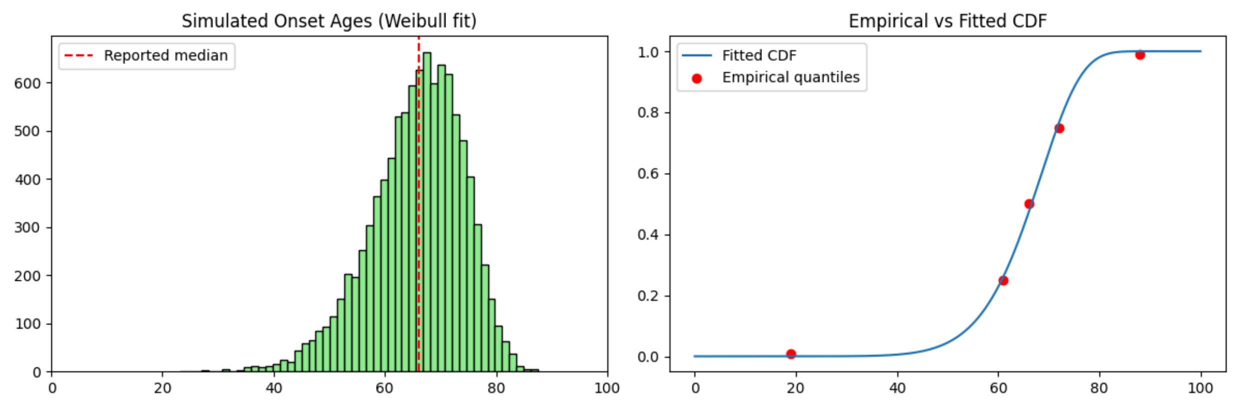
- `shape_fit_weibull` , `scale_fit_weibull` : The fitted shape and scale parameters

Simulate and visualize fitted distribution

In [ ]:
```
import matplotlib.pyplot as plt
```

In [43]:
```
# Simulate from fitted Weibull
sim_ages_weibull = weibull_min(c=shape_fit_weibull, scale=scale_fit_weibull).rvs(
```

In [57]:
```
# Plot histogram
fig, ax = plt.subplots(1,2, figsize=(12,4))

ax[0].hist(sim_ages_weibull, bins=50, color='lightgreen', edgecolor='black')
ax[0].axvline(x=median, color='red', linestyle='--', label='Reported median')
ax[0].set_xlim(0, 100)
ax[0].set_title('Simulated Onset Ages (Weibull fit)')
ax[0].legend()

# Plot empirical vs fitted CDF
x_weibull = np.linspace(0, 100, 300)
model_cdf_weibull = weibull_min(c=shape_fit_weibull, scale=scale_fit_weibull).cdf
ax[1].plot(x_weibull, model_cdf_weibull, label='Fitted CDF')
ax[1].scatter([min, q1, median, q3, max], [0.01, 0.25, 0.5, 0.75, 0.99], color='r
ax[1].set_title('Empirical vs Fitted CDF')
ax[1].legend()

plt.tight_layout()
plt.show()
```



Left panel shows the Weibull distribution of age at onset for anti-GABABR AIE, with the y-axis indicating patient counts. Right panel displays the cumulative distribution function (CDF) of the Weibull distribution alongside the empirical quantiles.

Fitting Generalized Gamma distribution

The generalized gamma distribution is a three-parameter family that encompasses many other distributions (e.g., exponential, Weibull, log-normal) as special cases.

- Why it's plausible: Its high flexibility makes it ideal for capturing heavy tails and non-standard skewness, especially when data are sparse or summary-based.
- Use case: Well-suited for modeling onset ages with substantial variation or heterogeneity.

Three parameters to fit in the generalized Gamma distribution:

- a: shape parameter
- c: power parameter
- scale: scale parameter

In [47]:
```
import numpy as np
from scipy.stats import gengamma
from scipy.optimize import minimize
```

In [48]:
```
# Define the quantile-matching objective function
def gengamma_objective(params):
    a, c, scale = params
    if a <= 0 or scale <= 0:
        return np.inf
    try:
        dist = gengamma(a=a, c=c, scale=scale)
        theo_q = dist.ppf([0.25, 0.5, 0.75])
        return np.sum((np.array(theo_q)- np.array(empirical_q))**2)
    except:
        return np.inf
```

In [50]:
```
# Run the optimization
initial_guess_gengamma = [2.0, 1.0, 10.0]
bounds_gengamma = [(0.01, None), (0.01, None), (0.01, None)]

result_gengamma = minimize(gengamma_objective, x0=initial_guess_gengamma, bounds=
a_fit_gengamma, c_fit_gengamma, scale_fit_gengamma = result_gengamma.x

print(f"Fitted Generalized Gamma parameters:\n a = {a_fit_gengamma:.3f}, c = {c_f
```

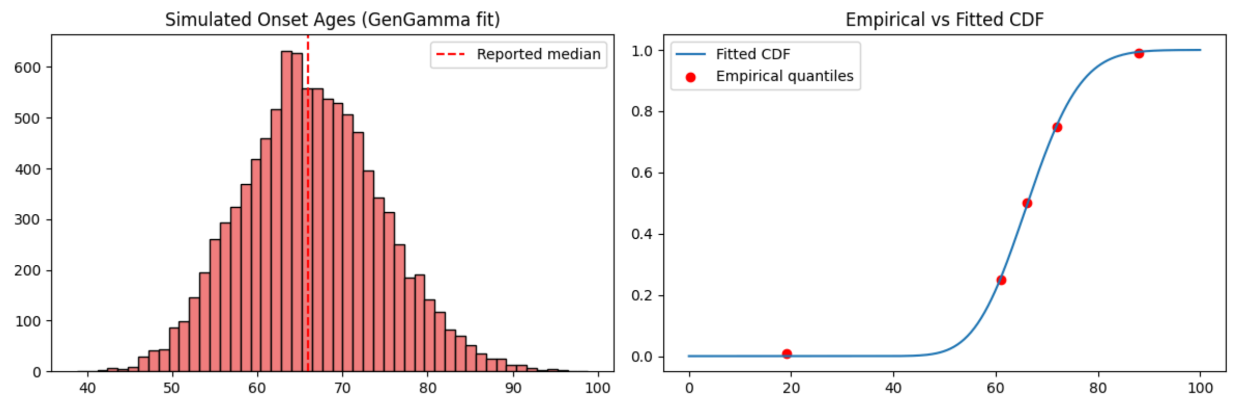
```
Fitted Generalized Gamma parameters:
 a = 26.611, c = 1.583, scale_fit_gengamma = 8.409
```

```
/var/folders/b8/9ymtxc2j7rb00xx34s753cwc0000gn/T/ipykernel_81972/1451994867.py:9:
RuntimeWarning: overflow encountered in square
  return np.sum((np.array(theo_q)- np.array(empirical_q))**2)
/opt/anaconda3/lib/python3.12/site-packages/scipy/optimize/_numdiff.py:590: Runti
meWarning: invalid value encountered in subtract
  df = fun(x) - f0
```

In [ ]:
```python
# Simulate and visualize
import matplotlib.pyplot as plt
```

In [52]:
```python
# Simulate onset ages
sim_ages_gengamma = gengamma(a = a_fit_gengamma, c = c_fit_gengamma, scale = scal
```

In [58]:
```python
# Plot histogram and CDF
fig, ax = plt.subplots(1, 2, figsize = (12, 4))

# Histogram
ax[0].hist(sim_ages_gengamma, bins=50, color='lightcoral', edgecolor='black')
ax[0].axvline(x=median, color='red', linestyle='--', label='Reported median')
ax[0].set_title('Simulated Onset Ages (GenGamma fit)')
ax[0].legend()

# CDF
x_gengamma = np.linspace(0, 100, 300)
model_cdf_gengamma = gengamma(a=a_fit_gengamma, c=c_fit_gengamma, scale=scale_fit
ax[1].plot(x_gengamma, model_cdf_gengamma, label='Fitted CDF')
ax[1].scatter([min, q1, median, q3, max], [0.01, 0.25, 0.5, 0.75, 0.99], color='r
ax[1].set_title('Empirical vs Fitted CDF')
ax[1].legend()

plt.tight_layout()
plt.show()
```



Left panel shows the generalized Gamma distribution of age at onset for anti-GABABR AIE, with the y-axis indicating patient counts. Right panel displays the cumulative distribution function (CDF) of the generalized Gamma distribution alongside the empirical quantiles.

Evaluate goodness-of-fit

Calculate the sum of squared differences between modelled and observed quantiles. Identify the best-fitting distribution.

In [60]:
```python
# Estimate quantiles from simulated age distributions
q25, q50, q75 = np.percentile(sim_ages, [25, 50, 75])

model_quantiles = np.array([q25, q50, q75])

# Calculate squared difference between modeled- and empirical quantiles
```

```
squared_diff = (model_quantiles - empirical_q) ** 2
sum_squared_diff = np.sum(squared_diff)
print(f"Sum of squared differences: {sum_squared_diff:.4f}")
```

```
Sum of squared differences: 0.0916
```

In [61]:
```
# Initialize dictionary for simulated age distributions
simulated_ages = {
    'lognormal': sim_ages,
    'weibull': sim_ages_weibull,
    'gengamma': sim_ages_gengamma
}

# Estimate quantiles for each distribution
quantiles = {}
for dist_name, ages in simulated_ages.items():
    q25, q50, q75 = np.percentile(ages, [25, 50, 75])
    quantiles[dist_name] = np.array([q25, q50, q75])
# Calculate squared differences between modelled and empirical quantiles
squared_diffs = {}
for dist_name, model_q in quantiles.items():
    squared_diff = (model_q - empirical_q) ** 2
    sum_squared_diff = np.sum(squared_diff)
    squared_diffs[dist_name] = sum_squared_diff
# Print the sum of squared differences for each distribution
for dist_name, sum_diff in squared_diffs.items():
    print(f"Sum of squared differences for {dist_name}: {sum_diff:.4f}")
```

```
Sum of squared differences for lognormal: 0.0916
Sum of squared differences for weibull: 0.5238
Sum of squared differences for gengamma: 0.0772
```

In this case, the Generalized Gamma distribution shows the smallest squared difference, indicating the best fit among the three candidate distributions.

Generalized gamma yields the smallest error, likely due to its flexibility in modeling both skew and kurtosis.

Estimate uncertainty

In this example, we aim to estimate how disease onset cases are distributed across three age groups: under 12, 12–17, and 18 or older. To go beyond simple point estimates, we apply bootstrapping—a resampling technique—to calculate not only the average proportion in each group but also 95% confidence intervals.

Why does this matter? Because decision-makers don’t just want the numbers—they want to know how certain we are. That’s exactly what bootstrapping reveals.

In [63]:
```
# Define age bands
age_bands = [(0,12), (12, 18), (18, 100)]

# Bootstrap settings
n_iterations = 1000
n_samples = 10000 # per bootstrap iteration
```

```
In [65]: # Bootstrap simulation
         bootstrap_results_gengamma = []

         for _ in range(n_iterations):
             sim_ages_gengamma2 = gengamma(a = a_fit_gengamma, c = c_fit_gengamma, scale =
             proportions = [np.mean((sim_ages_gengamma2 >= low) & (sim_ages_gengamma2 <= h
             bootstrap_results_gengamma.append(proportions)

         bootstrap_array_gengamma = np.array(bootstrap_results_gengamma)
```

```
In [68]: print(bootstrap_array_gengamma[:7])
```

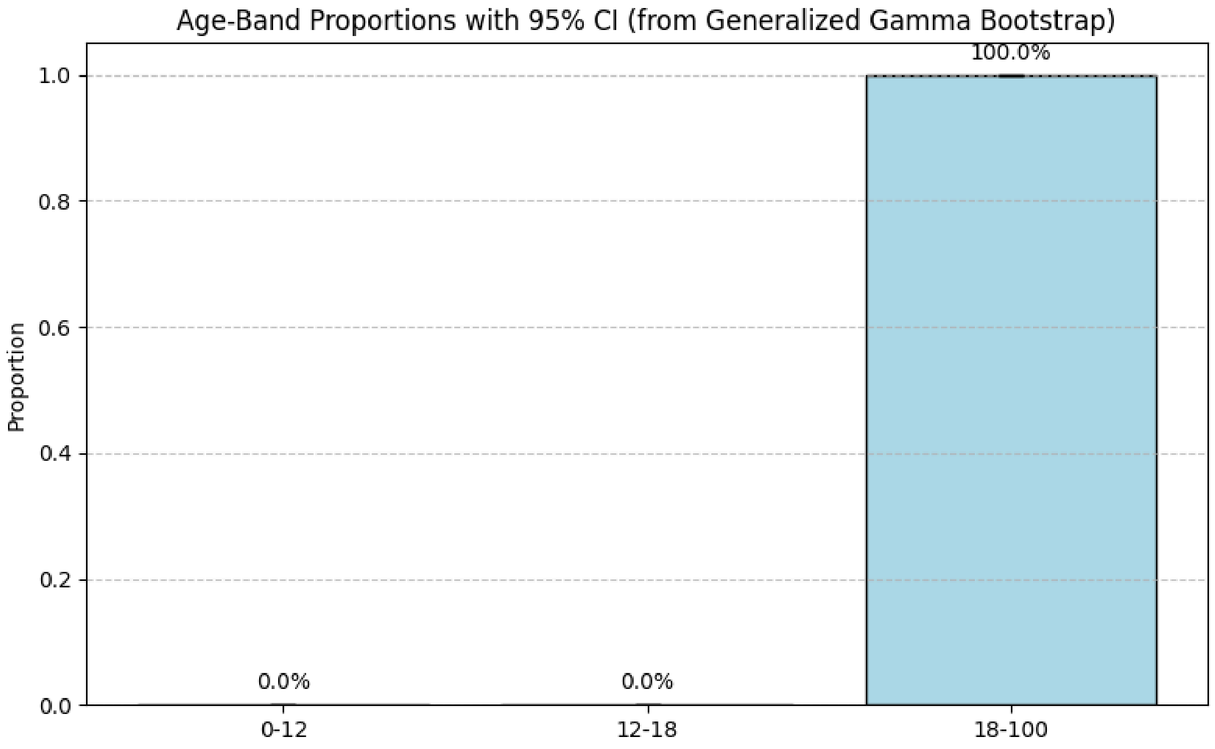
```
[[0.     0.     0.9999]
 [0.     0.     1.    ]
 [0.     0.     0.9999]
 [0.     0.     1.    ]
 [0.     0.     0.9999]
 [0.     0.     0.9998]
 [0.     0.     1.    ]]
```

```
In [70]: # Summarize results
         summary_gengamma = []
         for i, band in enumerate(age_bands):
             props = bootstrap_array_gengamma[:, i]
             summary_gengamma.append({
                 'Age Band': f'{band[0]}-{band[1]}',
                 'Mean Proportion': round(np.mean(props), 4),
                 '95% CI Lower': round(np.percentile(props, 2.5), 4),
                 '95% CI Upper': round(np.percentile(props, 97.5), 4)
             })


         df_summary_gengamma = pd.DataFrame(summary_gengamma)
         print(df_summary_gengamma)
```

```
  Age Band  Mean Proportion  95% CI Lower  95% CI Upper
0     0-12           0.0000        0.0000           0.0
1    12-18           0.0000        0.0000           0.0
2   18-100           0.9999        0.9997           1.0
```

```
In [71]: # Todo: Visualize mean proportion and 95% CI using a bar plot and error bars.
         import matplotlib.pyplot as plt
         import numpy as np

         # Extract data from DataFrame
         labels = df_summary_gengamma["Age Band"]
         means = df_summary_gengamma["Mean Proportion"]
         ci_lower = df_summary_gengamma["95% CI Lower"]
         ci_upper = df_summary_gengamma["95% CI Upper"]

         # Calculate error bars
         error_lower = np.maximum(means - ci_lower, 0)
         error_upper = np.maximum(ci_upper - means, 0)
         error = [error_lower, error_upper]

         # Create bar plot with error bars
         fig, ax = plt.subplots(figsize=(8, 5))
         bars = ax.bar(labels, means, yerr=error, capsize=6, color='lightblue', edgecolor=
```

```python
# Annotate percentages
for i, bar in enumerate(bars):
    height = bar.get_height()
    ax.annotate(f"{height:.1%}",
                xy=(bar.get_x() + bar.get_width() / 2, height),
                xytext=(0, 5),
                textcoords="offset points",
                ha='center', va='bottom')

# Format the plot
ax.set_ylabel("Proportion")
ax.set_title("Age-Band Proportions with 95% CI (from Generalized Gamma Bootstrap)
ax.set_ylim(0, 1.05 * ci_upper.max())
ax.grid(axis='y', linestyle='--', alpha=0.7)

plt.tight_layout()
plt.show()
```



Age-band–specific proportions of anti-GABABR AIE patients estimated using a generalized gamma distribution

Practical Guidance

This notebook provides a reusable template. When adapting to other diseases, ensure clinical plausibility of candidate distributions and interpret tail behavior carefully.