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Population Generation via Resampling

Curtis K. Johnston

How are populations made in the “wild?”

Dad, where do populations come from?

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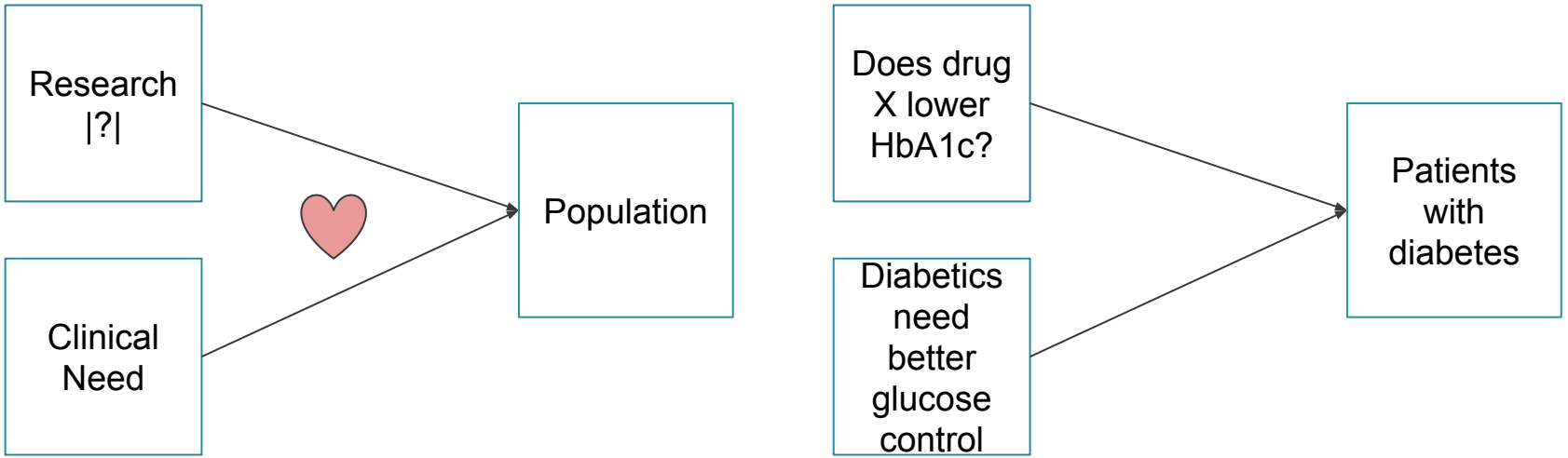
- **Well, when a research question and a clinically relevant need love each other, very much……..**



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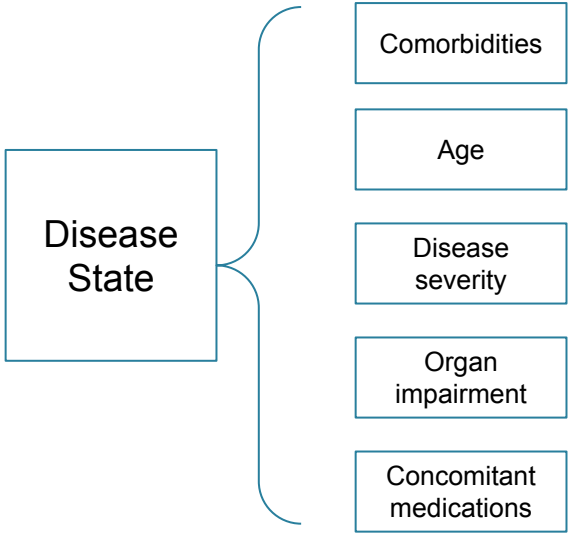
How are populations made in the “wild?”

A population is defined by the question being asked and the clinical need being addressed.



Our selection on these criteria are what defines the population.

(Study Exclusion/inclusion) (PMR)…

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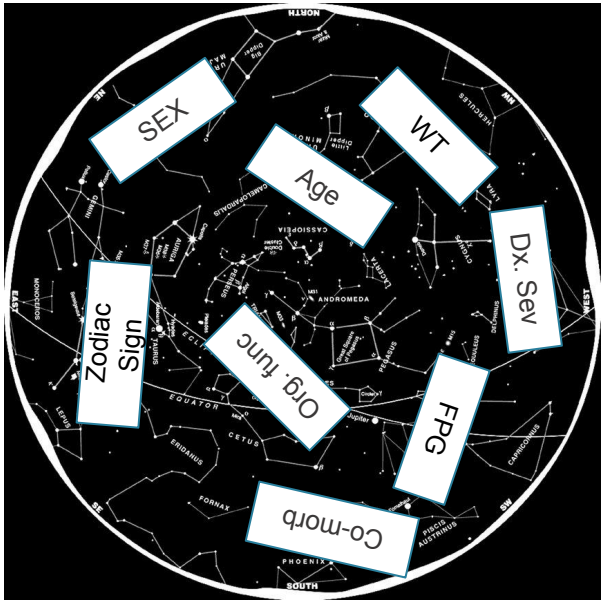
How are populations made in the “wild?”

These and “other” covariates form a conditional multivariate constellation.

- Comorbidities
- Age
- Disease severity
- Organ impairment
- Concomitant medications



This distribution seems complicated…

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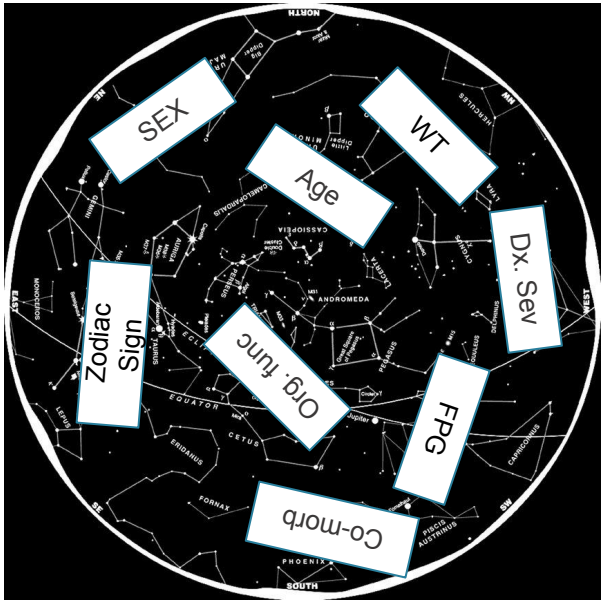

This distribution seems complicated…

IT IS!

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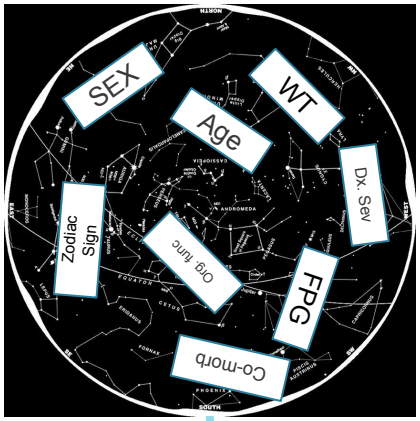
How are populations made *de novo*?

Luckily, we don't need to know the data-generating distribution in order to create a population that follows the distribution!



Resampling allows us to generate a population that maintains the underlying distribution

ID	SEX	WT	DX	FPG	CM	AGE	ZS	ORF
1	1	75	1	72	1	37	S	Mod
2	0	98	2	87	0	45	T	Mild

ID	SEX	WT	DX	FPG	…
X1	1	75	1	72	…
X2	0	98	2	87	…

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How are populations made *de novo*?

In most instances resampling from you analysis population should suffice, but when won't it?

- **If the population of interest is not well represented in your analysis dataset**
  - 50-70 per category of interest would be ideal, but even these rules are not well defined (Dosne 2016)
  - Sometimes this is all you have and you just acknowledge the limitation

- **If the population of interest is not represented (at all) in your analysis dataset**
  - Use publicly available research datasets (NHANES)

What is NHANES?

National Health and Nutrition Examination Survey (NHANES)

- Survey research program that collect longitudinal data on medical data and physiological measurements (lab data)
  - Surveys have been conducted annually since 1999 (first conducted in 1971)

- Survey results are publicly available; either directly from the NCHS website or via convenient R packages.
  - https://www.cdc.gov/nchs/nhanes/index.htm
  - nhanesA (R package)

What do you need to do before diving in?

First, we must define our question!!!

Ideally, this helps you define your sampling criteria…

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Let's imagine an example!

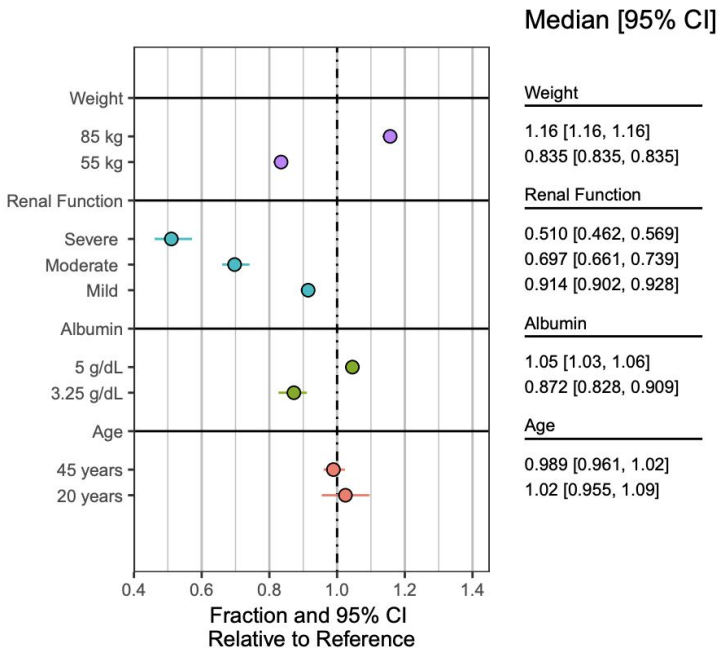
Example PopPK analysis

- You have conducted a PopPK analysis…
  - 2-CMT model, first-order absorption…
  - Allometrically scaled weight on CL/F and V/F parameters
  - Covariate effects for eGFR, AGE, and ALB

$$
\begin{aligned}
CL/F_i &= e^{(\theta_3+\mathrm{CL/F}_{WT}+\mathrm{CL/F}_{eGFR}+\mathrm{CL/F}_{AGE}+\mathrm{CL/F}_{ALB}+\eta_{3i})} \\
\mathrm{CL/F}_{WT} &= 0.75 \cdot ln(\mathrm{WT}_i/70) \\
\mathrm{CL/F}_{eGFR} &= \theta_6 \cdot ln(\mathrm{eGFR}_i/90) \\
\mathrm{CL/F}_{AGE} &= \theta_7 \cdot ln(\mathrm{AGE}_i/35) \\
\mathrm{CL/F}_{ALB} &= \theta_8 \cdot ln(\mathrm{ALB}_i/4.5)
\end{aligned}
\qquad (16)
$$

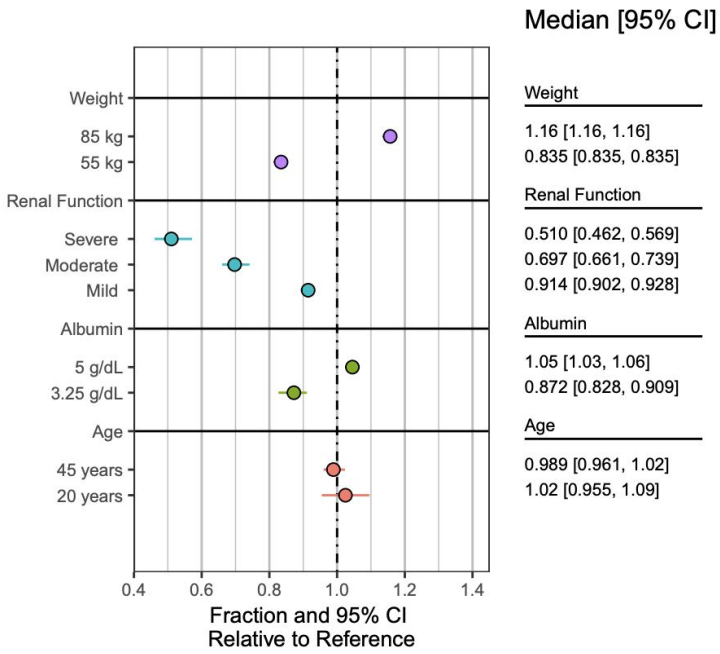
Example PopPK analysis

- "May" be a signal for eGFR on CL/F…
  - Development team wants to know if dose adjustment is warranted….
  - So….what's the question?



Example PopPK analysis

- Do I need to adjust the dose in clinically identifiable sub-populations?
  - KDIGO subgroups
  - *Want to assess of the causal effect of dose in these subpopulations, not the causal effects of covariates.*
- How are you defining your margins (efficacy/safety)?
  - Not addressing here, but relevant in real world examples
- Dose adjustment or exclusion of use?



Example PopPK analysis

- We want to conduct population-level simulations for each subgroup of interest and contrast exposures at available dose levels.
- We can normalize to a reference, if desired, otherwise, just contrast exposure ranges

Simulation map

	Model Parameters, Measurable & Uncontrollable Factors	Design	N
Uncertainty (u)	θ (CL, V, V2, Q, KA, Cov) , Ω (Ka, V, CL)	Bootstrap	1000
Population/Trial (p)	Clinically relevant sub-population (θ_i:1000)	NHANES	6
Individual (i)	Weight (kg), Age (y), eGFR (CKDEPI), Alb (g/dL) (η_Ka, η_V, η_CL)	10 and 25 mg @ SS	1000
Occasion (k)			
Observation (t)	AUC_{SS} = (Dose/CL_i)	Median 90 % CI	1000 (x6)

Go to hands on example and walkthrough code

- pk-sim-renal.R
  - Script that generates the virtual populations of interest using NHANES
  - Simulates exposures for them according to the simulation map
  - Summarizes the exposures
  - Generates summary plots

References

- Dosne AG, Niebecker R, Karlsson MO. dOFV distributions: a new diagnostic for the adequacy of parameter uncertainty in nonlinear mixed-effects models applied to the bootstrap. J Pharmacokinet Pharmacodyn. 2016 Dec;43(6):597-608. doi: 10.1007/s10928-016-9496-7. Epub 2016 Oct 11. PMID: 27730481; PMCID: PMC5110608.
- NHANES: https://www.cdc.gov/nchs/nhanes/index.htm