# HoLISTIC Multistate Model (MSM) Working Group Meeting

5/10/24

# Outline

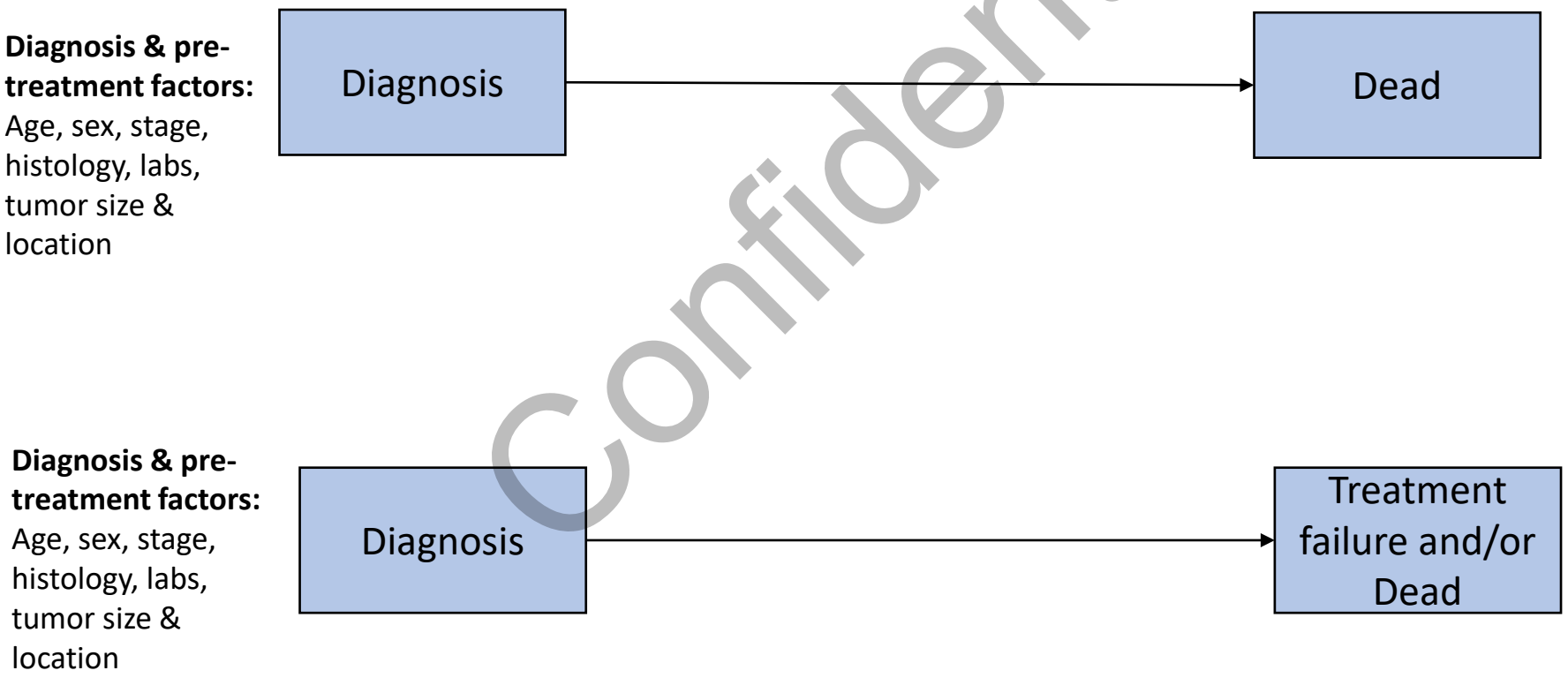
- Big picture & introduction to MSM
- Inclusion/exclusion criteria
- Baseline characteristics & outcomes by treatment arm
- Very preliminary MSM results
- Next steps

**Disclaimer: all results are very preliminary as we are still cleaning the data, but we wanted to begin testing the model.*

# Big picture

- Goal of this analysis is to predict outcomes for a future patient based on baseline disease characteristics and treatment
- First MSM iterations (through 5 years) will be based on clinical trials because outcomes are adjudicated, and we have detailed information about treatment (dates, dosages)
  - We will start with time-invariant treatment regimens (ECOG2496, HD2000, HD9601, Stanford V); these all have response based on CT scan
- Separate models for early and advanced stage trials
  - We will start with advanced stage trials

# Reminder: we already built prediction models using pre-treatment factors & one outcome per model (A-HIPI, E-HIPI)

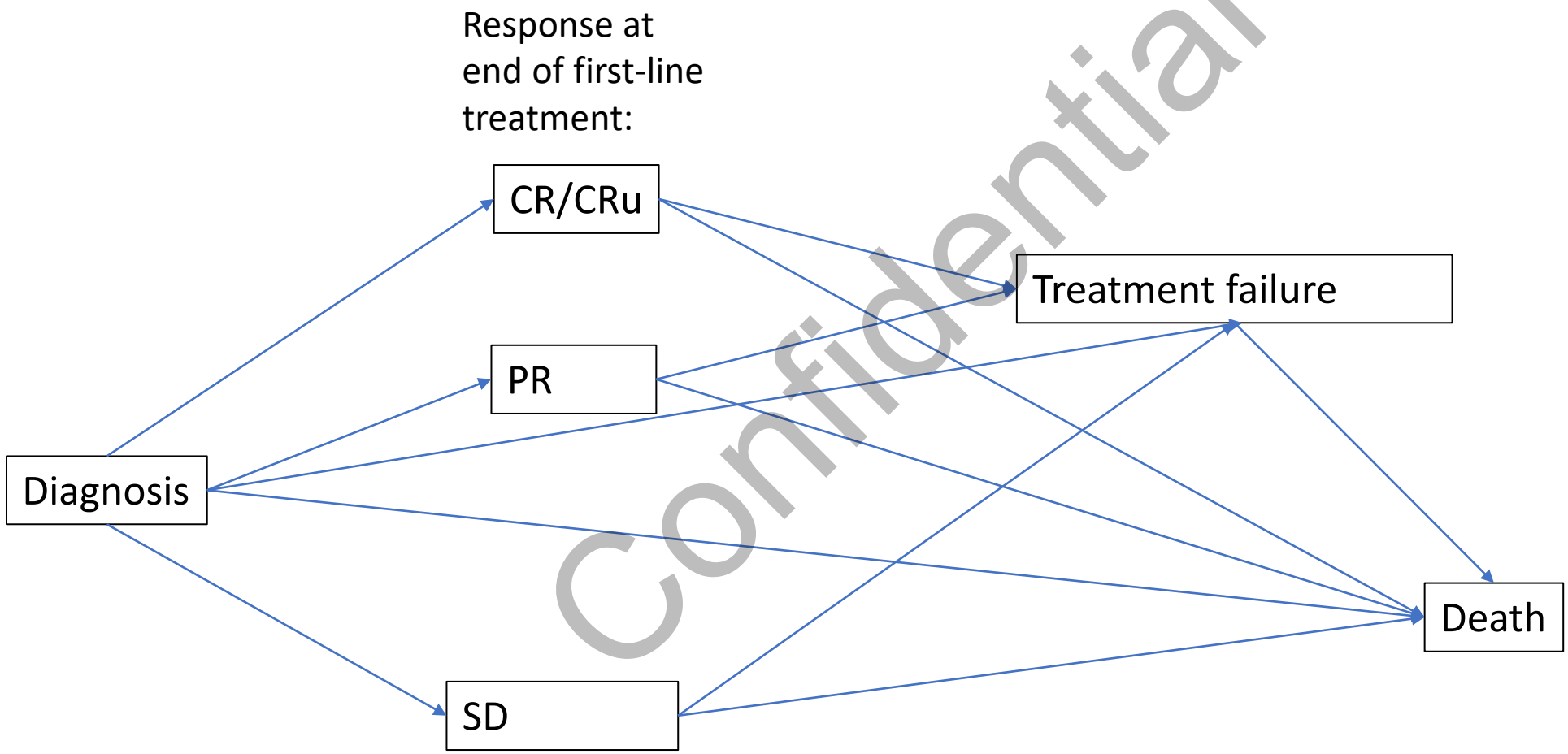


# Advantages of MSM

- Allows us to incorporate different disease states
  - Deals with the issue of non-informative censoring & competing risks
    - *Survival analysis assumes censoring is non-informative or independent, meaning that censored patients have similar outcomes as those who remain in the study.*
    - *Violated when competing events prevent occurrence of an event of interest (e.g., death prevents occurrence of relapse).*
    - *Furthermore, intermediate, non-fatal events that influence risk of future event (e.g., relapse changes risk of death) can also violate this assumption.*
- Estimates transition probabilities between disease states
  - Can have different covariates for each transition
- We will add treatment to the MSM

# 3-state MSM (“illness-death model”)

# MSM incorporating treatment response






CR=complete response; PR=partial response; CRu=complete response-unconfirmed aka complete clinical response; SD=stable disease; PD=progressive disease

# Current inclusion/exclusion for advanced stage MSM

- Inclusion
  - cHL
  - Age 18 to 65y
  - Advanced stage trials with time-invariant treatment regimens
  - Stage IIB, III, IV

- Exclusion
  - No treatment received
  - Extended field RT only
  - Those treated with regimens no longer used (e.g., COPP/MOPP-like regimens)
  - Those with inevaluable end-of-treatment scans

# Baseline characteristics by treatment arm, n=1579

**Disclaimer: all results are very preliminary as we are still cleaning the data, but we wanted to begin testing the model.*

| | ABVD, n=805 | BEACOPP, n=89 | Stanford V, n=685 |
|---|---|---|---|
| Study, n (%) | | | |
| 1ECOG2496 | 407 ( 50.6) | 0 ( 0.0) | 403 ( 58.8) |
| 5HD2000 | 95 ( 11.8) | 89 (100.0) | 0 ( 0.0) |
| 6HD9601 | 109 ( 13.5) | 0 ( 0.0) | 99 ( 14.5) |
| 13StanfordV | 194 ( 24.1) | 0 ( 0.0) | 183 ( 26.7) |
| Age (years), mean (SD) | 34.64 (11.62) | 33.08 (11.40) | 34.85 (11.39) |
| Female, n (%) | 370 ( 46.0) | 35 ( 39.3) | 305 ( 44.5) |
| Stage, n (%) | | | |
| Stage IIB | 206 ( 25.8) | 26 ( 29.2) | 172 ( 25.2) |
| Stage III | 285 ( 35.8) | 44 ( 49.4) | 241 ( 35.3) |
| Stage IV | 197 ( 24.7) | 19 ( 21.3) | 155 ( 22.7) |
| B symptoms, n (%) | 520 ( 66.2) | 65 ( 73.0) | 420 ( 63.2) |

(currently there is variable-level missingness in these tables; multiple imputation not yet been applied)

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| | ABVD, n=805 | BEACOPP, n=89 | Stanford V, n=685 |
|---|---|---|---|
| Histology, n (%) | | | |
| Lymphocyte depleted | 5 ( 0.6) | 3 ( 3.4) | 4 ( 0.6) |
| Lymphocyte rich | 11 ( 1.4) | 3 ( 3.4) | 11 ( 1.6) |
| Mixed cellularity | 79 ( 9.8) | 7 ( 7.9) | 64 ( 9.3) |
| Nodular sclerosis | 550 ( 68.3) | 68 ( 76.4) | 466 ( 68.0) |
| NOS | 50 ( 6.2) | 7 ( 7.9) | 50 ( 7.3) |
| Any bulk[a], n (%) | 400 ( 55.0) | 48 ( 53.9) | 327 ( 53.9) |
| WBC count (10^3/uL), mean (SD) | 9.64 (5.28) | 10.74 (5.14) | 9.65 (5.74) |
| Lymphocyte count (10^3/uL), mean (SD) | 1.43 (0.77) | All missing | 1.35 (0.72) |
| Hemoglobin (g/dL), mean (SD) | 12.08 (1.84) | 11.53 (2.01) | 11.98 (1.94) |
| Albumin (g/dL), mean (SD) | 3.72 (0.63) | 3.57 (0.67) | 3.70 (0.66) |
| ESR (mm/hr) (subset only), mean (SD) | 58.62 (36.28) | 71.75 (36.85) | 58.95 (36.45) |

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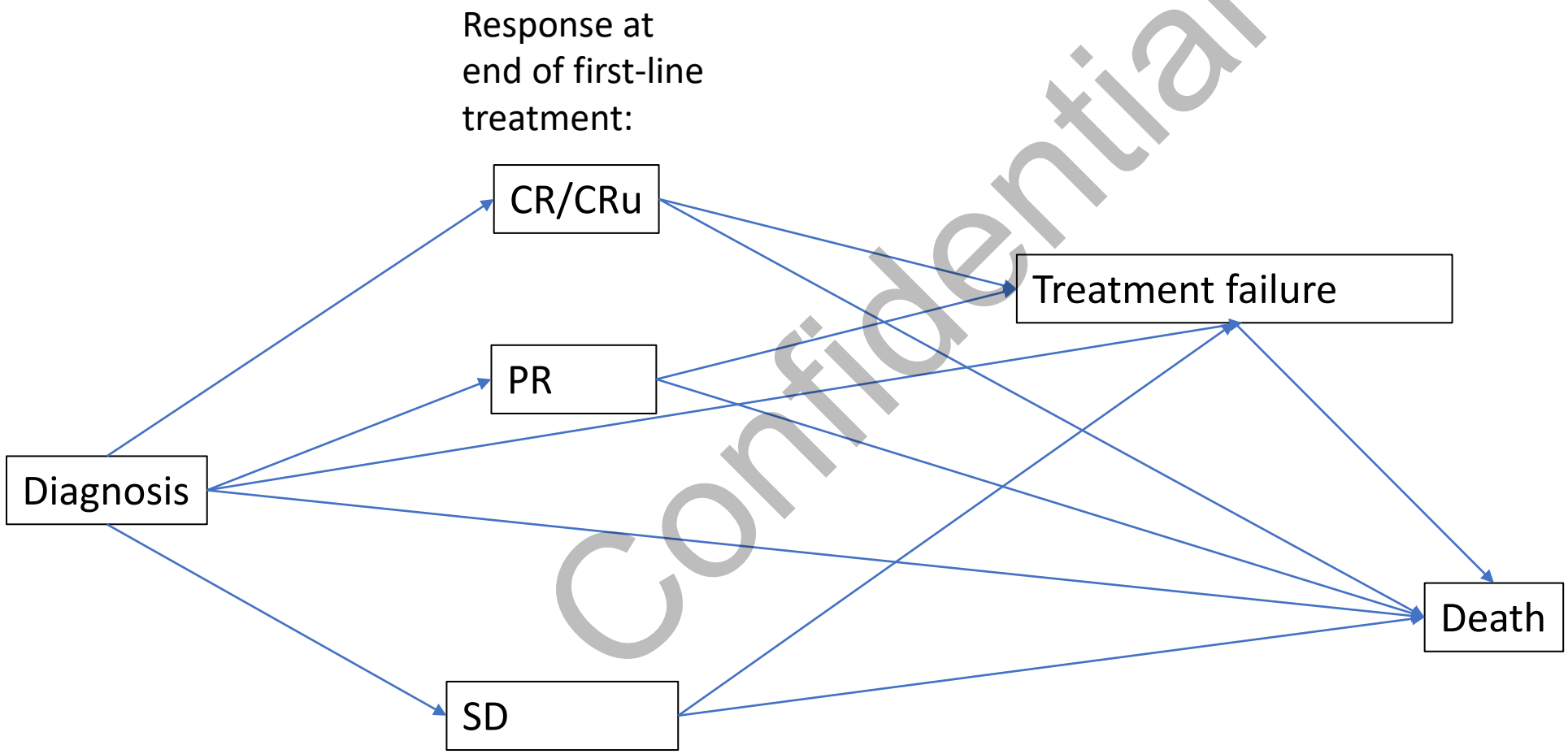
# Outcomes by treatment arm

| | ABVD, n=805 | BEACOPP, n=89 | Stanford V, n=685 |
|---|---|---|---|
| **Outcomes** | | | |
| **Treatment response, n (%)** | | | |
| **CR/CRu** | 527 ( 71.4) | 81 ( 95.3) | 315 ( 51.1) |
| **PR** | 141 ( 19.1) | 3 ( 3.5) | 190 ( 30.8) |
| **SD/PD** | 70 ( 9.5) | 1 ( 1.2) | 111 ( 18.0) |
| **No treatment response information** | 67 | 4 | 69 |
| **Treatment failure by 5 years, n (%)** | 149 ( 18.5) | 13 ( 14.6) | 156 ( 22.8) |
| **Death by 5 years, n (%)** | 69 ( 8.6) | 8 ( 9.0) | 71 ( 10.4) |



To do: Look at overlap between trt failure & death; look at PFS

# MSM incorporating treatment response



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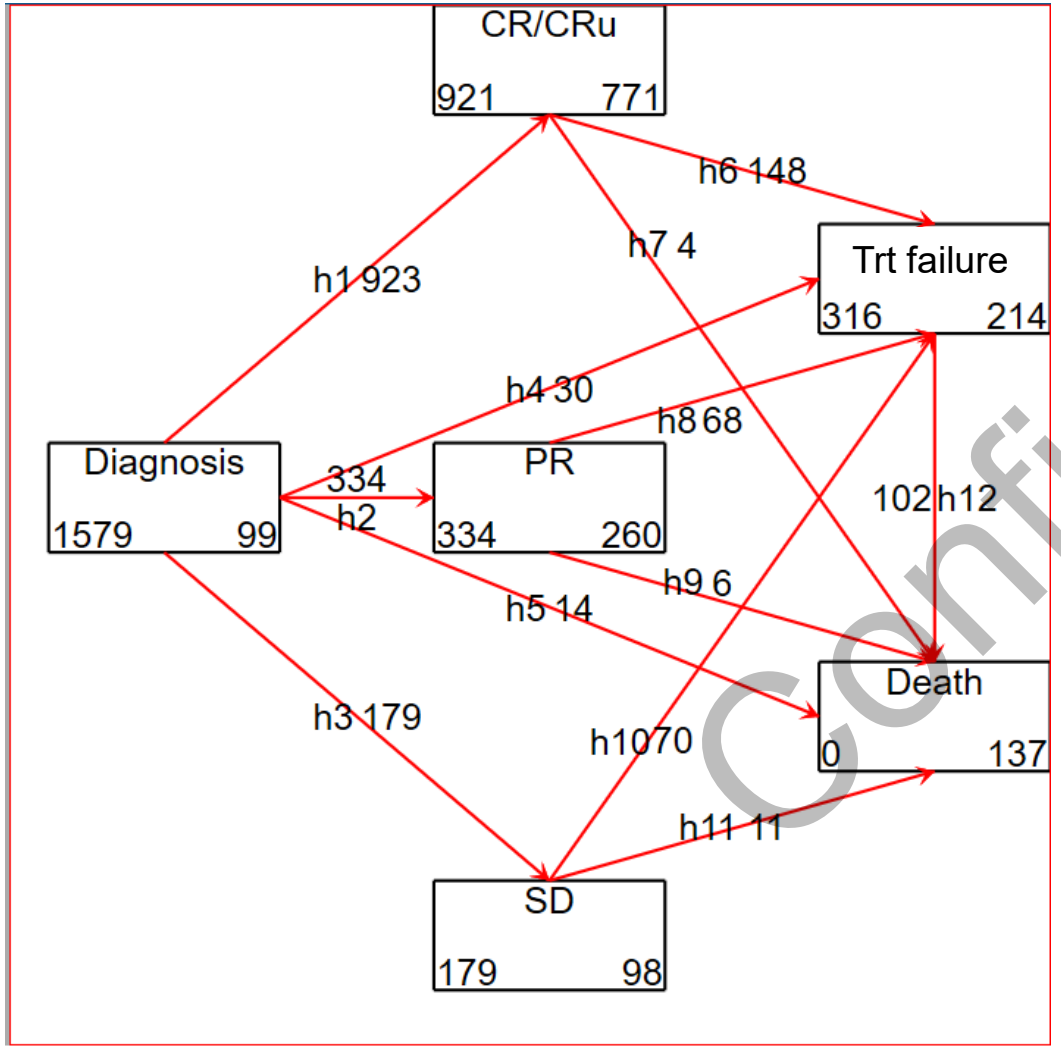
# MSM incorporating treatment response




- Challenges:
  - Small Ns for some transitions
  - Estimated hazard ratios based on this model were unstable

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# State occupancy for MSM incorporating treatment response

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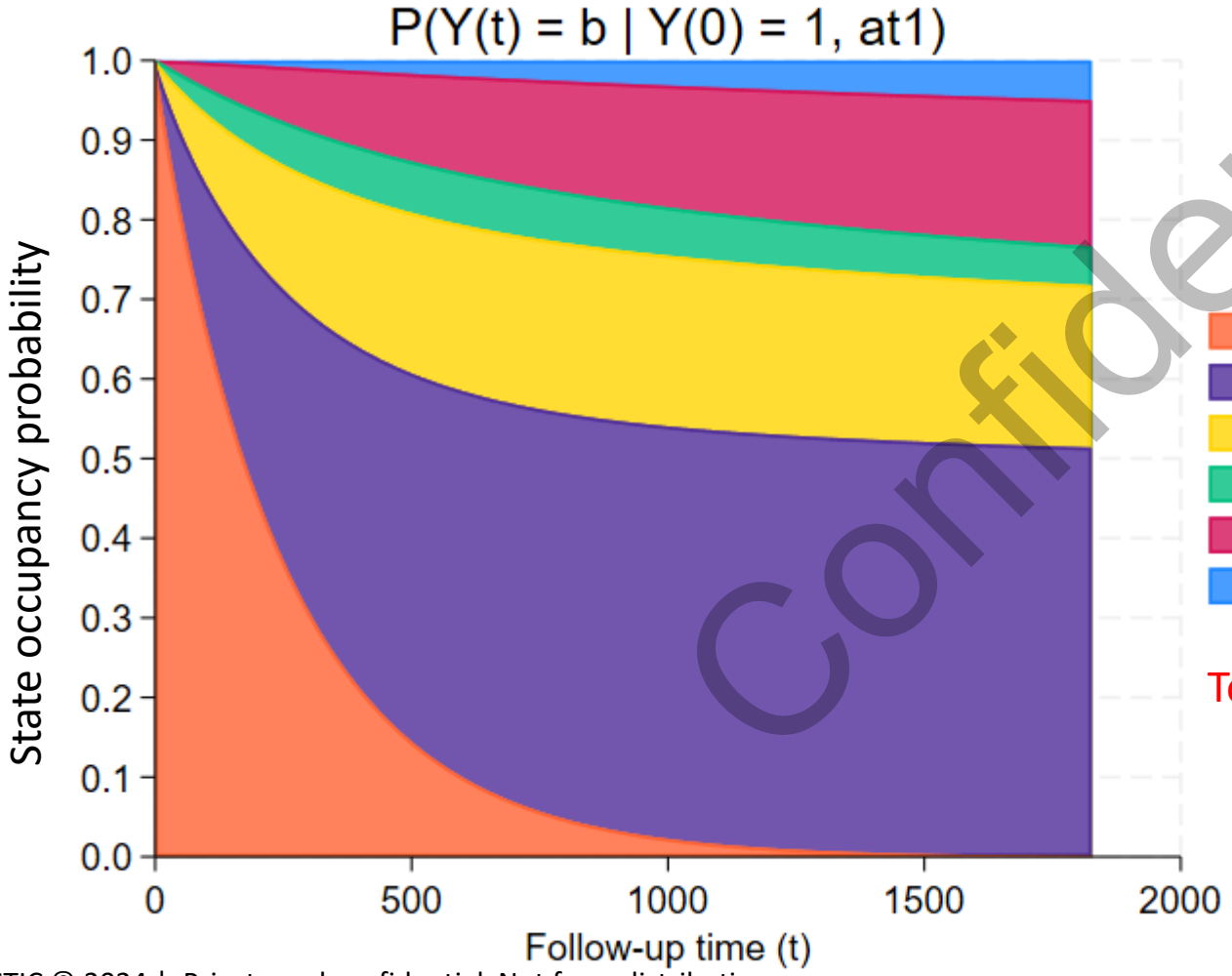


P(Y(t) = 1 | Y(0) = 1) State 1= Diagnosis
P(Y(t) = 2 | Y(0) = 1) State 2= CR/CRu
P(Y(t) = 3 | Y(0) = 1) State 3=PR
P(Y(t) = 4 | Y(0) = 1) State 4=SD
P(Y(t) = 5 | Y(0) = 1) State 5=Trt failure
P(Y(t) = 6 | Y(0) = 1) State 6=Death

To do: We will censor those in dx stage at end of trt

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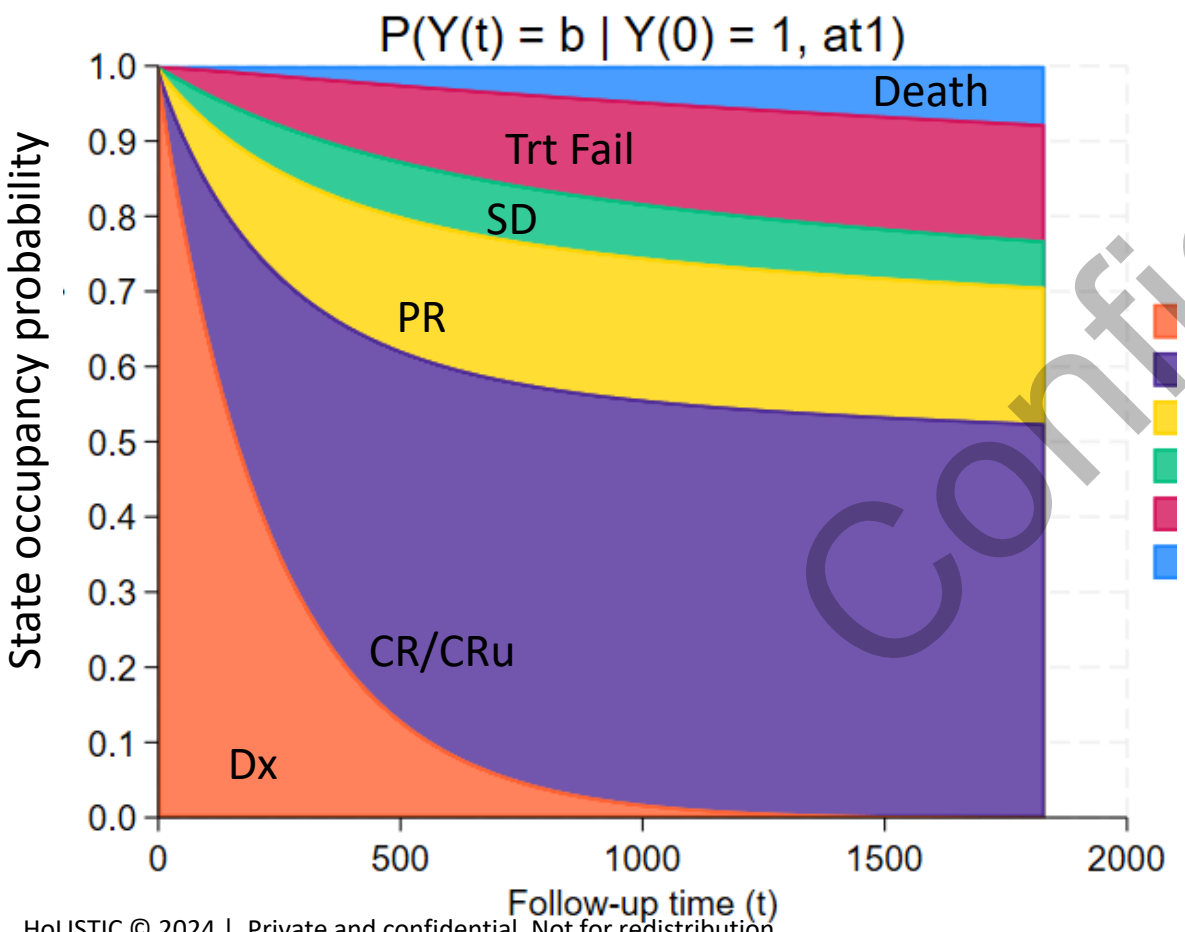
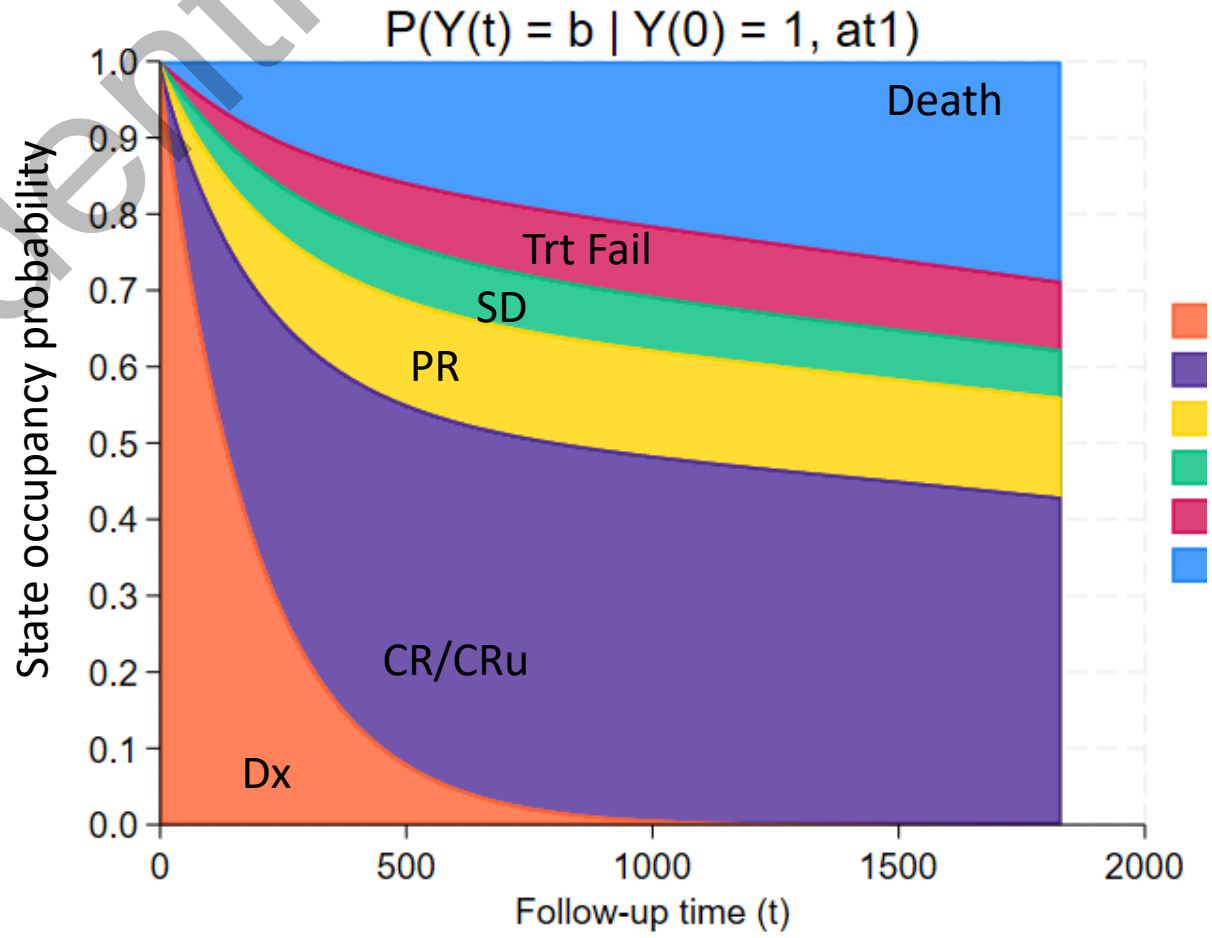
# State occupancy for MSM incorporating treatment response by age

To do: We will censor those in dx stage at end of trt

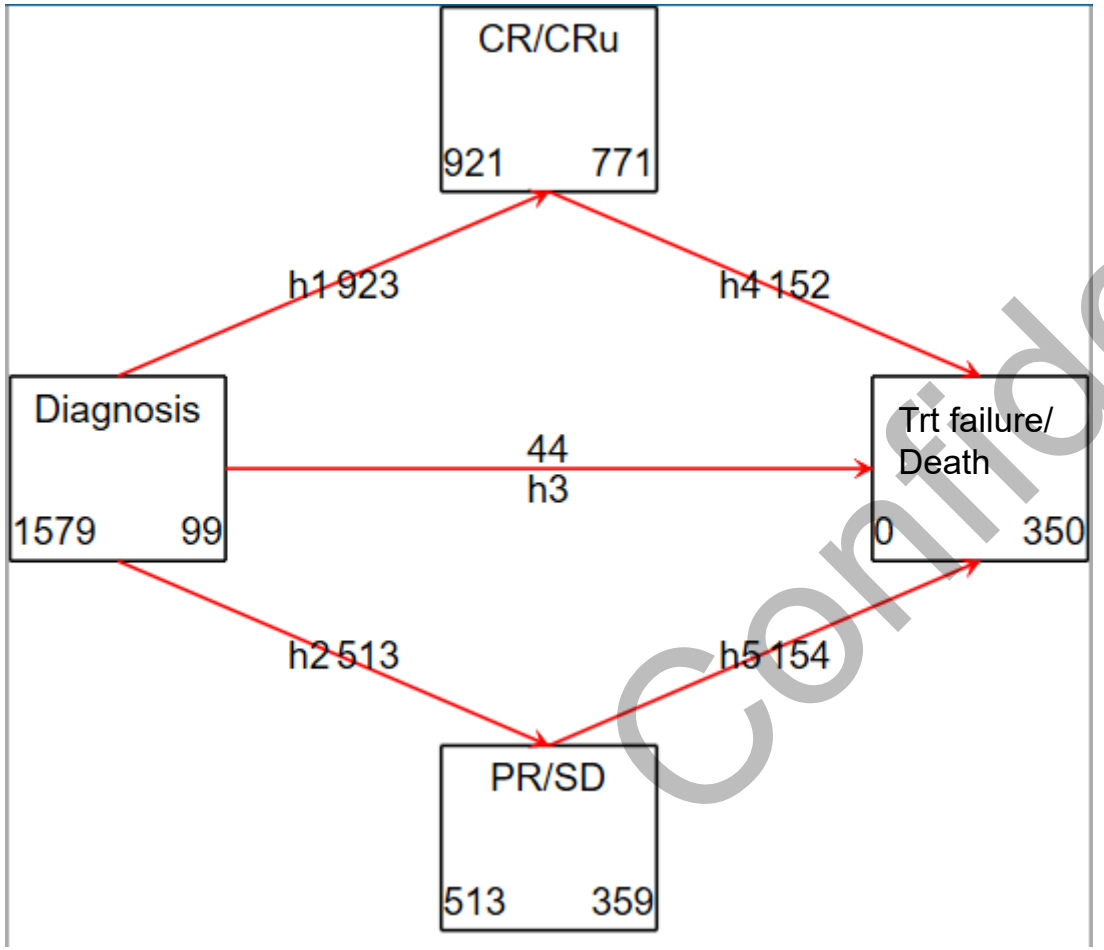
**Age 30**




**Age 65**



# MSM incorporating treatment response & combining some states

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# Next steps

- Near term
  - Continue data cleaning and refining model structure
  - Impute missing data
  - Incorporate other covariates (e.g., age, AHIPI score)
    - Model building strategy; could use AHIPI in first transitions out of dx
  - Prepare ASH abstract (no tables/figures)

- Long term
  - Incorporate trials with PET-adaptive, time-varying treatment regimens
    - RT (y/n)
  - Validation of model results
  - Incorporate relapse/refractory & post-acute adverse effects
    - More detailed treatment variables here (e.g., chemo dose, RT site/dose)

# MSM Members as of May 10, 2024

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