A Case Study Using Nature History Data to Understand Long-Term Disease Progression

In rare disease world

Those who fail to learn from historical data fail to understand your drug

Disclaimers

- For confidentiality considerations, all data presented here has been processed by adding a random error term to the individual patient data
- The focus of this presentation is to demonstrate the application but not the numerical results; the conclusion of this presentation may or may not reflect that of the real project
- The opinions expressed in this presentation and on the following slides are solely those of the authors and not necessarily those of Biogen

Part I: Regulatory environment

21 Century Cures Act passed in 2016

21 USC 355g.

"SEC. 505F. UTILIZING REAL WORLD EVIDENCE.

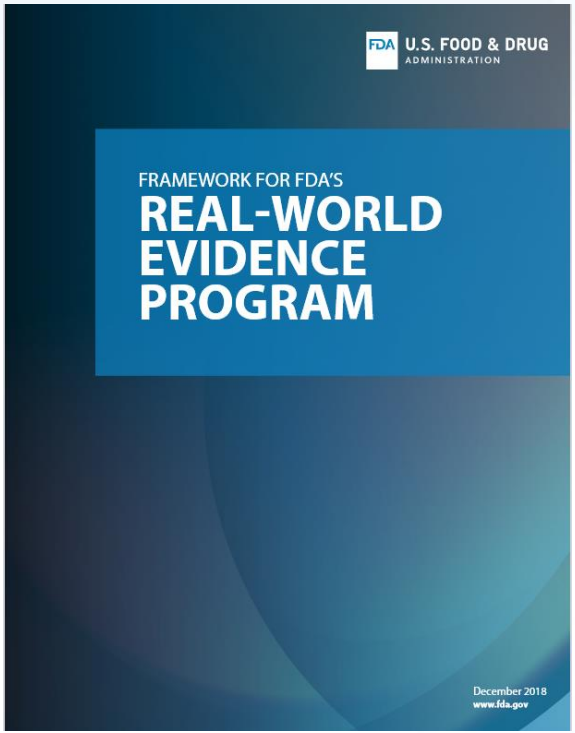
"(a) IN GENERAL.—The Secretary shall establish a program to evaluate the potential use of real world evidence—

"(1) to help to support the approval of a new indication for a drug approved under section 505(c); and

"(2) to help to support or satisfy postapproval study requirements.

"(b) REAL WORLD EVIDENCE DEFINED.—In this section, the term 'real world evidence' means data regarding the usage, or the potential benefits or risks, of a drug derived from sources other than randomized clinical trials.

RWE program published in Dec 2018



- Draw distinction between RWD and RWE
- Evaluation of RWE need to take into consideration of the methodology and the reliability and relevance of the RWD
- The framework addresses both data and study design/methodology to utilize the data

FDA Guidance on Human Gene Therapy on Rare Disease

If a single-arm trial design with a historical control is necessary, then knowledge of the natural history of disease is critical. Natural history data may provide the basis of a historical control, but only if the control and treatment populations are adequately matched, in terms of demographics, concurrent treatment, disease state, and other relevant factors. In circumstances where randomized, concurrent-controlled trials cannot be conducted and the natural history is well characterized, sponsors may consider the clinical performance of available

Two examples from FDA approvals

- On 4 April 2019, the FDA announced its extension of the indication of Ibrance (palbociclib) in combination with endocrine therapy for HR-positive, HER2-negative advanced or metastatic breast cancer in men, based on an analysis of real-world data, specifically from electronic health records (EHRs) and post-marketing reports
- On July 3, 2019, the Food and Drug Administration granted AA to selinexor (XPOVIO, Karyopharm Therapeutics) in combination with dexamethasone for adult patients with relapsed or refractory multiple myeloma (RRMM) who have received at least four prior therapies. RWE was used to compare with single arm trial using propensity score matching
  - The evidence generated from RWD was deemed as inadequate
  - https://www.fda.gov/media/121667/download (appendix 10.1)

Part II: Case Study RWE used to support clinical development

Our problem: The disease

- Slow progressive rare disease
- Primary endpoint: change from baseline in scores from 0-100
- **Challenge**: unknown **long term** disease progression trend
- **Goal:** Use natural history data to explore long term treatment effect

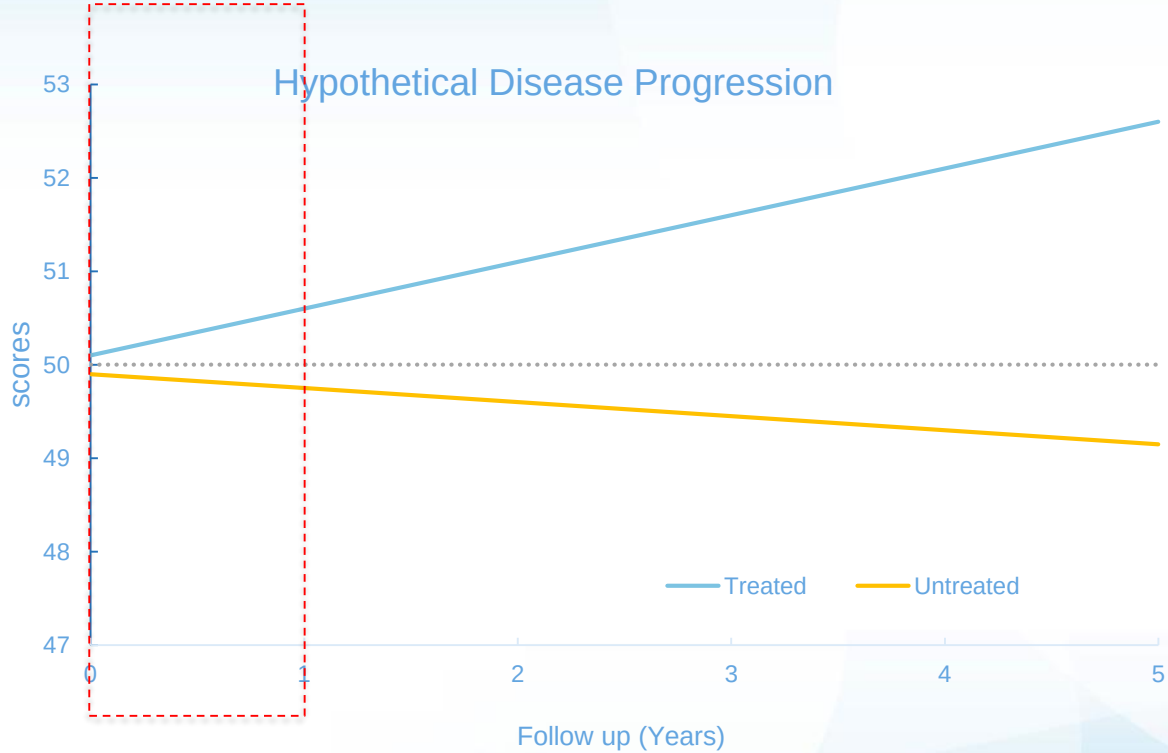
Feedback from Regulatory

- External control can not be used for submission for the division approached
- Lesson: Innovative design is more acceptable in rare disease division

What data we have

- Randomized clinical trials focusing on intermediate term – 12 months treatment effect with both treated and untreated patients (not available yet)
- Randomized clinical trials data might be extended to 5 years of follow up for treated patients but 3 years for the untreated patients (not available yet) – mitigation plan
- **Investigator sponsored trial (IST) has 24 months of follow up (available now)**
- **Natural history study (NHS) has 20 months of follow up (available now)**

Study Rationale



- Use IST and NHS as a ‘pilot’ to understand the long-term treatment effect for internal discussions before other data is available
- What’s the treatment effect at 5-year F/U?

The plan

- Step 1: Understand the general trend/assumption – meta-analysis from literatures
- Step 2: Understand the disease progression using natural history data (propensity score matching)
- Step 3: Project long term disease progression focusing on matched untreated patients

Step 1: Meta-analysis

1. Identify publications reporting patient-level data by age in the literature

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2. Extract patient-level data from articles (directly from tables or using software to extract from figures)

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3. Create a database: Literature extractions + internal natural history data

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4. Conduct statistical analysis to understand outcome score trends by age

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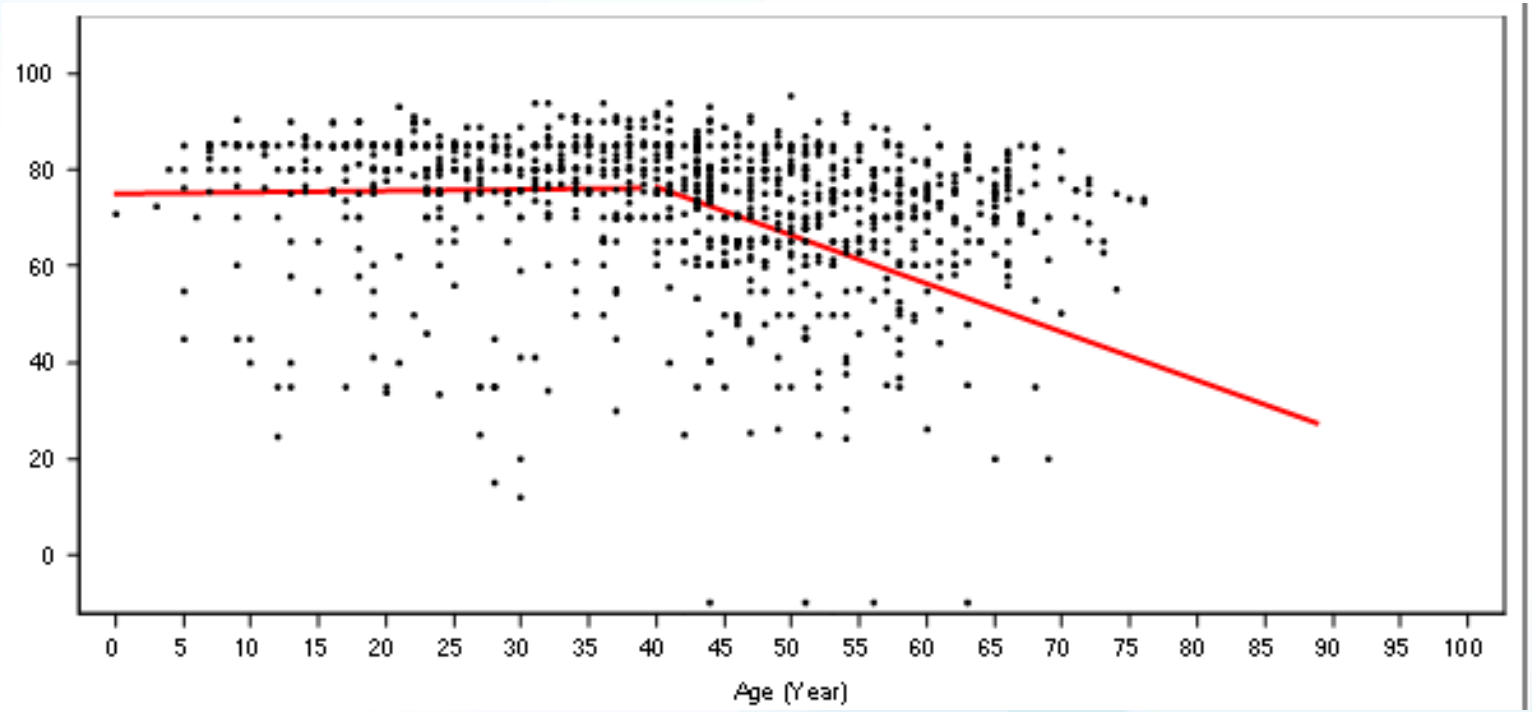
5. Identify an age cutoff where the disease starts to progress more quickly (segmented regression)

Meta-Analysis

- Findings from the individual literatures are mostly based on cross-sectional data with scores and age
- A finding from the meta-analysis is that disease progression seems to be slower in younger patients, and faster in older patients

Segmented regression: Cutoff of Age is roughly around 40 years old



Cross-sectional data from 1037 subjects in 23 studies

Step 2: Propensity Score Matching

- Investigator initiated trial (IST) with 24 months of follow up (N = 32)
- Natural history study (NHS) with 20 months of follow up (N = 319)
- Consistent I/E criteria from the two studies
- Variables to be matched: age, baseline Score, race, country, baseline imaging variable 1, baseline imaging variable 2

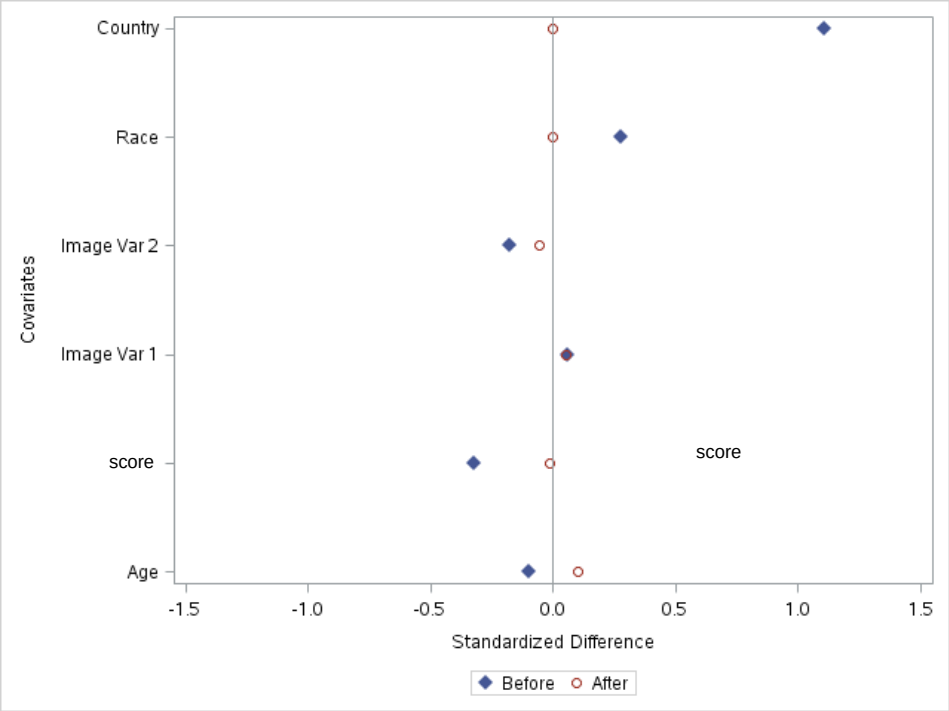
Propensity Score Matching

- 1:1 Greedy Matching with and without caliper
  - Using difference between the PS (caliper width) equal to 0.2 to avoid pairing dissimilar individuals.
  - Results presented are based on matching without caliper
- 1:2 matching (where 1:1 to 5 were also explored as sensitivity analysis
- Sensitivity analyses include different matching methods: PS stratification; IPTW with stabilized weight

Patient Characteristics before and After Matching

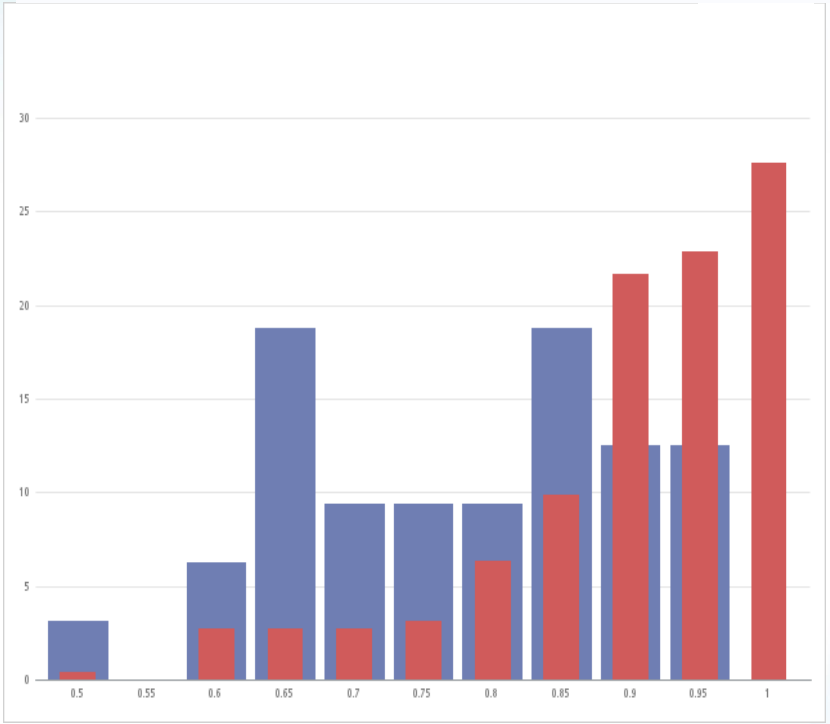
Baseline Characteristics	Study IST		NHS Study		NHS Study After Matching		Standardized Difference	
	Mean or N	SD or %	Mean or N	SD or %	Mean or N	SD or %	Before Matching	After Matching
Age	47.6	11.93	46.4	13.51	46.7	14.08	-0.0979	0.0960
Baseline score	75.6	10.12	72.4	9.71	72.7	13.02	-0.3214	-0.0131
Imaging variable 1	118.6	68.92	122.5	65.94	122.0	64.82	0.0568	0.0528
Imaging variable 2	4.2	3.78	3.4	4.67	3.4	5.13	-0.1790	-0.0571
Race							0.2768	0.0000
Asian	1	3.1%	2	0.8%	2	3.1%		
Native American	0		1	0.4%				
Black	0		1	0.4%				
Native Hawaiian Or Other Pacific Islander	0		1	0.4%				
White	31	96.9%	246	96.9%	62	96.9%		
Other	0		3	1.2%				
Country							1.1051	0.0000
Canada	6	18.8%	19	7.5%	12	18.8%		
Germany	6	18.8%	48	18.9%	12	18.8%		
UK	14	43.8%	40	15.8%	28	43.8%		
USA	6	18.8%	84	33.1%	12	18.8%		
Brazil	0		13	5.1%				
Denmark	0		4	1.6%				
Finland	0		29	11.4%				
France	0		11	4.3%				
Netherland	0		6	2.4%				

Matching diagnosis – Standardized difference

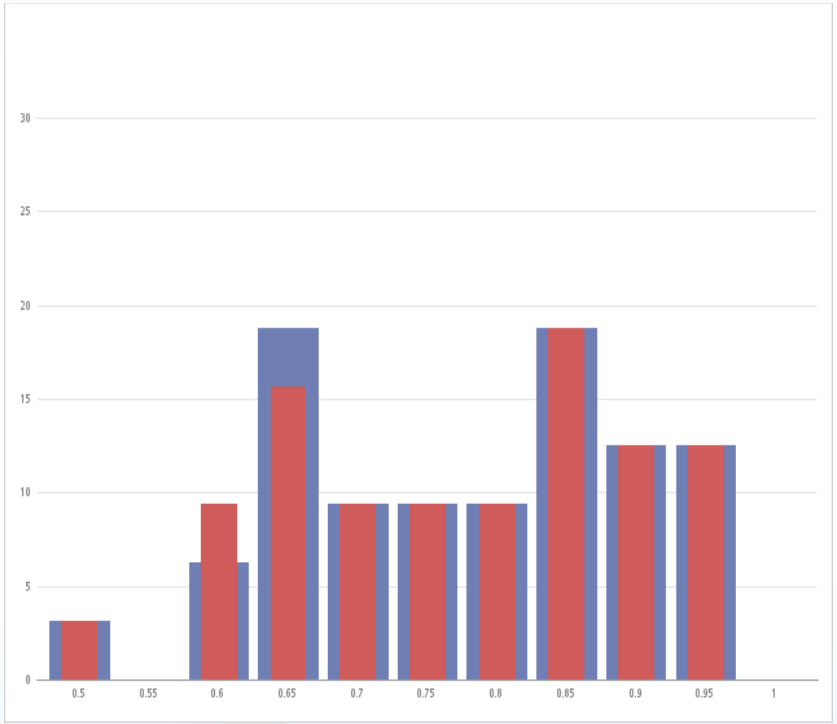


Distribution of Propensity Scores Pre- and Post-Match

Pre-Match



Post-Match



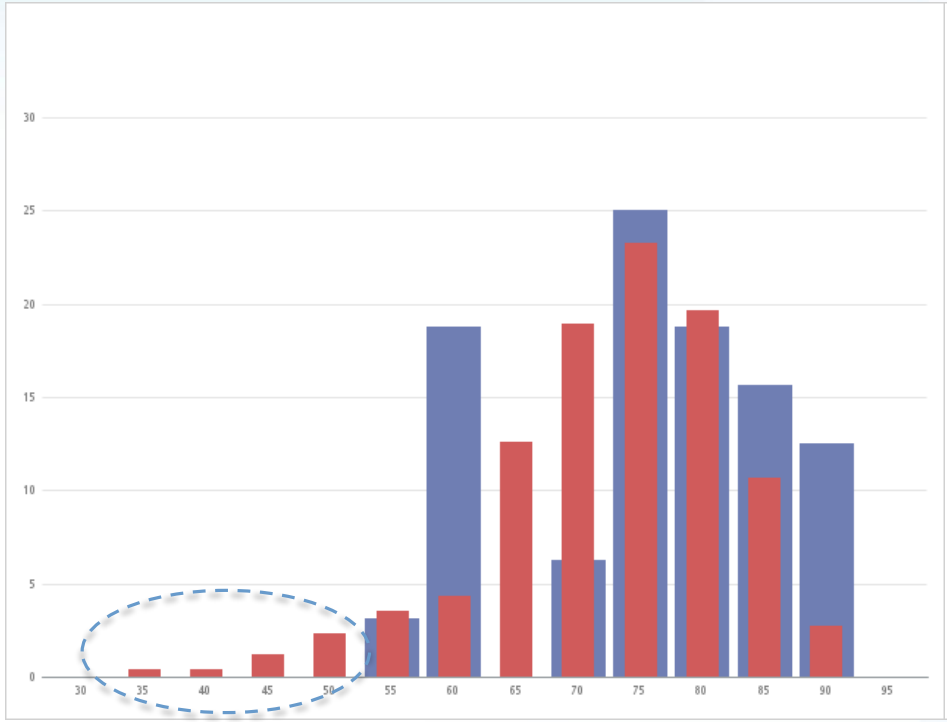
IST

NHS

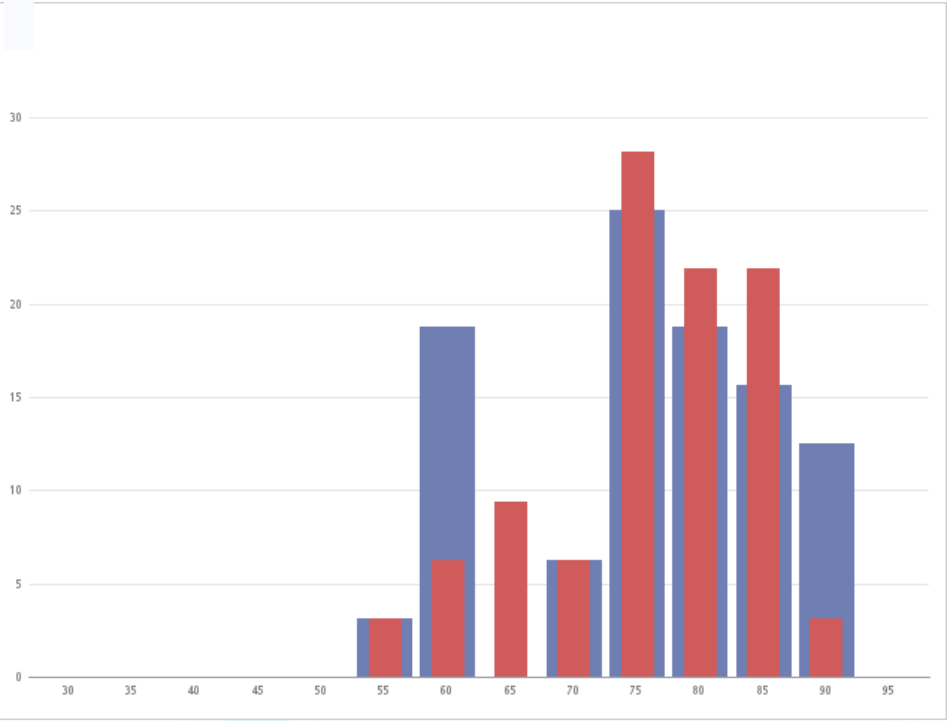
Y axis is the percent of subjects in that interval. X axis is the propensity score.

Distribution of Baseline Outcome Score Pre- and Post-Match

Pre-Match



Post-Match



IST

NHS

Y axis is the percent of subjects in that interval. X axis is the propensity score.

Step 3: Projection based on the matched analysis for treatment comparison at Year 5

Model	N	Treatment Difference at Year 5	95% CI	p-value
Unadjusted	351	1.9021	(-0.6194, 4.4239)	0.1401
PS Matching	96	6.7103	(0.7224, 12.6981)	0.0287
Sensitivity analysis				
PS Stratification	351	2.7876	(0.6434, 4.9318)	0.0114
IPTW with Stabilized Weight	351	1.7334	(-0.2304, 3.6973)	0.0847

- Conclusions and trends are generally consistent across different PS methods
- PS matching has relatively larger variance due to smaller sample size, also with larger treatment effect as a trade-off
- IPTW is controversial: fail to reduce imbalance and bias (Liu, Q., Castelli, J., and Hoodbrook, F. (2019). Statistical analysis of single-arm trial with virtual matched controls. *Technical Document)*

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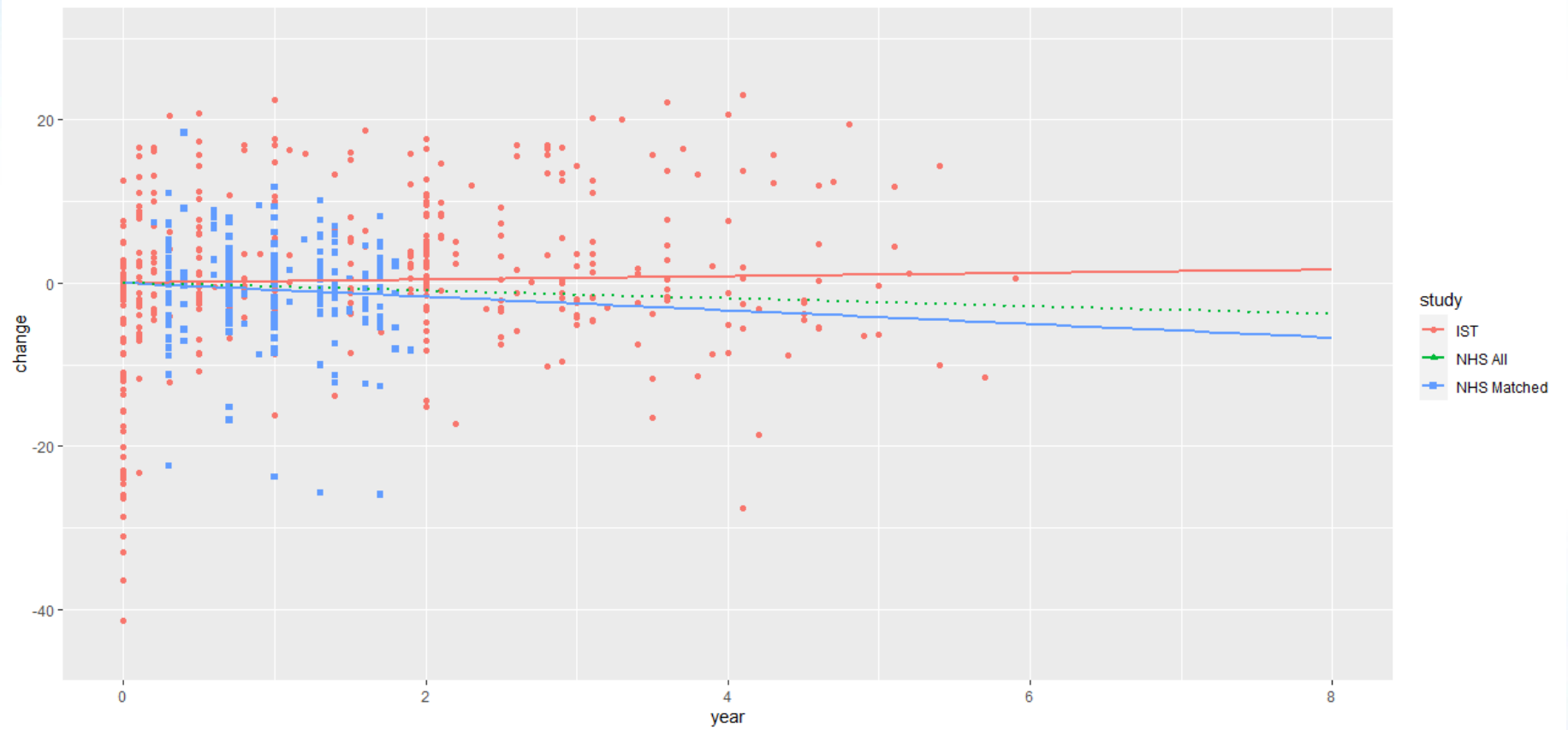
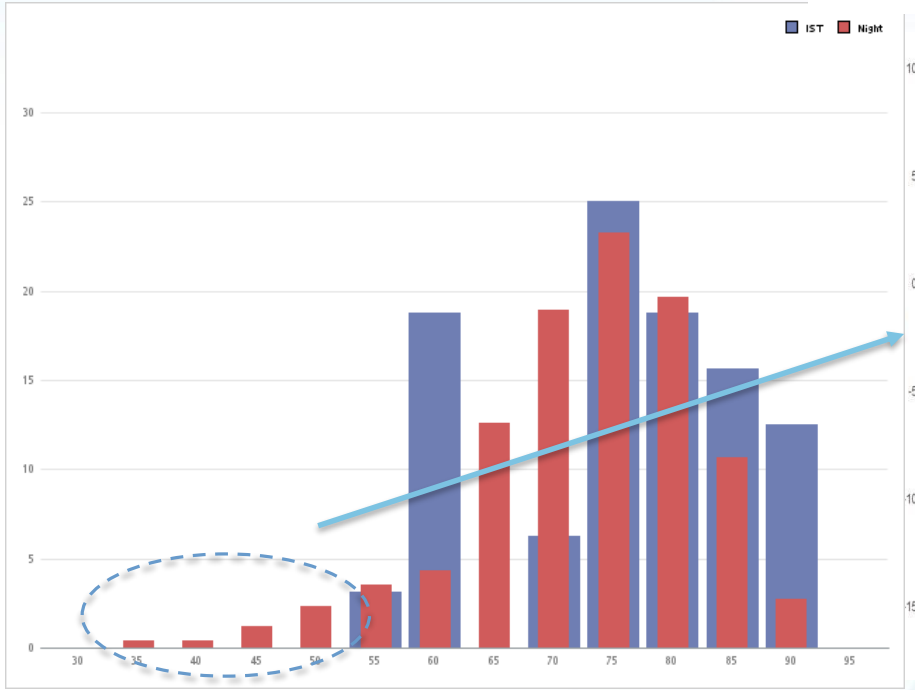
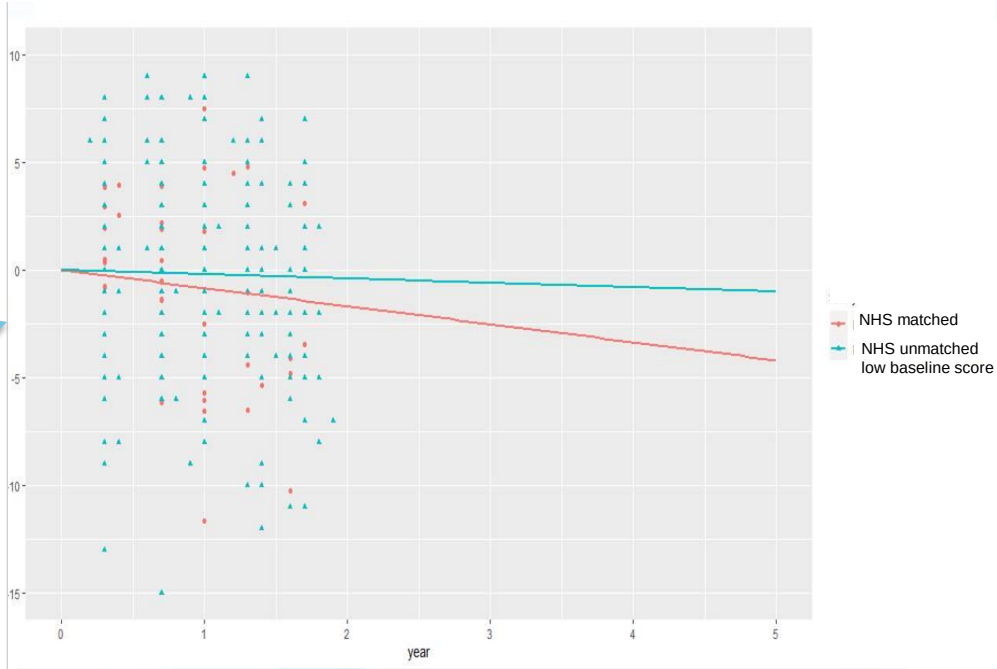
Change from Baseline Projection



“Floor” effect from NHS may explains why

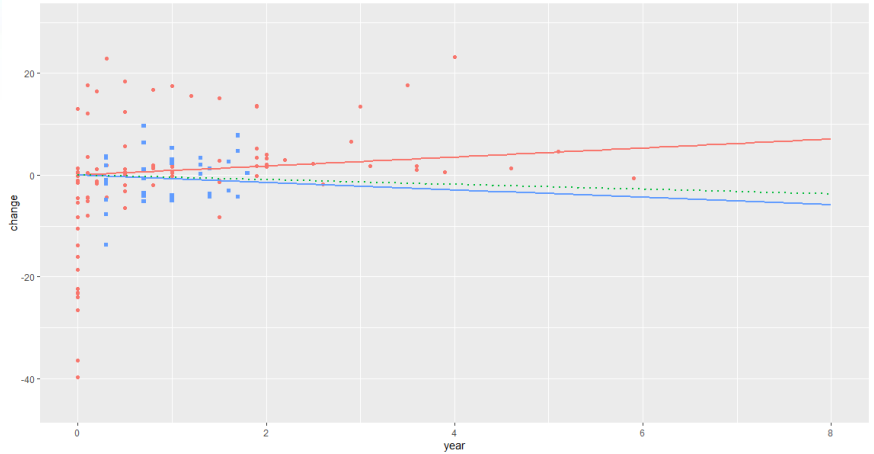




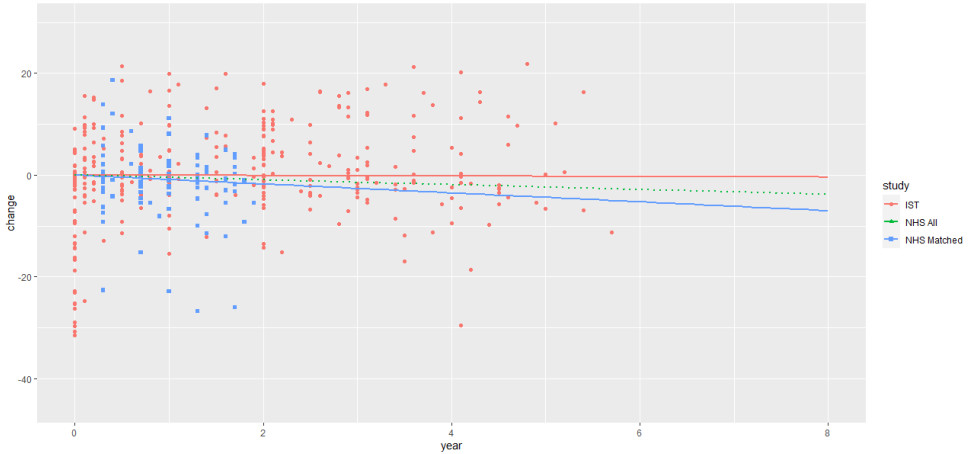
IST
NHS

Change from Baseline Projection by age

Age<40



Age>=40



- Due to accelerated disease progression after age 40, patient's improvement is not as desirable as that for age < 40
- Treatment effect is less in younger age than older age

Limitations

- PS matching can not eliminate the impact from unmeasured confounders; Limited variables in common from the two studies
- PS matching cannot overcome initial selection bias
- King, G. and Nielson, R. (2019) criticized PSM mimic complete randomization rather than block randomization or stratified randomization
- Projection is based on linear extrapolation, which may not capture the potential secondary progression after x number of years F/U

Planned Further Activities

- Further analysis using NHS and randomized study when it's ready (hybrid design)
- Registry data provides longer term of follow up on untreated patients (~5 years)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