# Does Clinical Evidence of Heterogeneity Influence Treatment Selection? A Case Study of Abiraterone for Metastatic Hormone-Sensitive Prostate Cancer

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## Evidence-Based Medicine

- In the era of evidence-based medicine, findings from randomized clinical trials (RCTs) form the foundation of medical evidence
- RCT results can inform clinical guidelines and translate into a change in clinical practice in oncology
- Previous studies explored cancer treatment pattern changes associated with the evidence of average treatment benefits or harms from RCTs
- Few studies have explored whether the **evidence of treatment effect heterogeneity**— usually found through **subgroup analyses** in RCTs— leads to **differential cancer treatment utilization** across subgroups

## Case: Abiraterone

- We focused on the case of abiraterone acetate plus prednisone (AAP) as a treatment for metastatic hormone-sensitive prostate cancer (mHSPC)
- Two pivotal phase 3 RCTs: LATITUDE[1] and STAMPEDE[2]
  - Released by New England Journal of Medicine in June 2017
  - AAP combined with androgen deprivation therapy (ADT) significantly extends the survival of men with mHSPC versus ADT alone
  - Subgroup analyses: survival benefits of ADT + AAP were larger for **younger versus older men** — hazard ratio was not statistically significant for those aged ≥75 years old in LATITUDE and ≥70 years old in STAMPEDE
- The RCTs' findings led to FDA approval and an upgraded guideline recommendation of AAP as a treatment for mHSPC
- The evidence of heterogeneity in terms of age was not incorporated in the product label or clinical guidance
- To date, it is still not clear whether such evidence of treatment effect heterogeneity might influence the real-world utilization of AAP despite the absence of relevant clinical guidance

## Objective

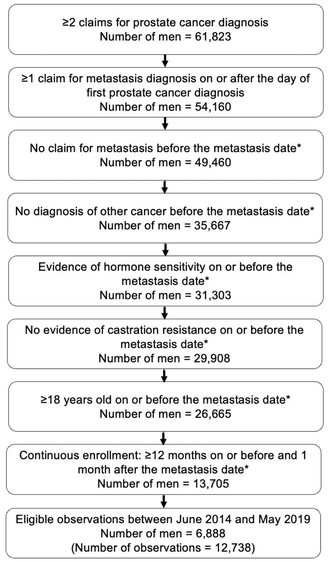
- To assess whether **publication of the RCTs** was associated with **differential AAP uptake** between **younger and older** mHSPC men in the US.

## Data

- We used electronic medical records (EMR) data from TriNetX platform (TriNetX, Inc., Cambridge, MA)
  - Collected from 43 healthcare organizations across the US
  - Including demographics, diagnoses, medications, procedures, and lab test results
- We included all the eligible observations from June 2014 (three years before the publication) to May 2019 (two years after the publication)

## Study Population

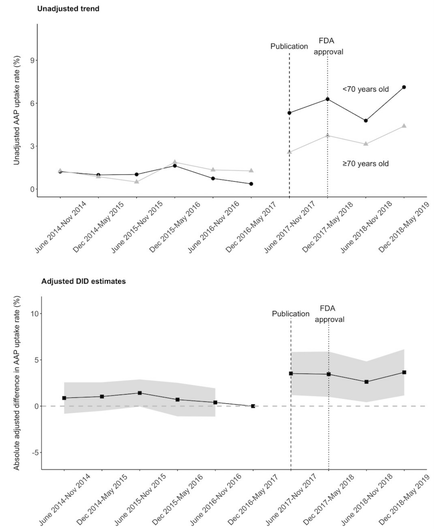
- We retrospectively identified an eligible US cohort of men with newly diagnosed mHSPC based on a comprehensive, sensitive algorithm developed by Freedland et al.[3]




## Difference-in-Differences

- Our study assessed the uptake rate of AAP: % of men with newly diagnosed mHSPC who initiate AAP during a six-month period
  - The numerator: men initiating AAP during this period
  - The denominator: men at risk of initiating AAP when entering this period
- Statistical model
  - A difference-in-differences (DID) event study to assess the differential utilization of AAP between age groups before versus after publication of the RCTs
  - A linear generalized estimating equation with an exchangeable correlation structure to account for within-subject correlation and a robust standard error estimator
- Dependent variable:
  - Binary variable indicating whether initiating the AAP or not during the given period
- Independent variables:
  - Time fixed effects (the period before publication as reference)
  - Age group of < 70 years old
  - Interactions between the fixed time effects and age group
  - Race, region, comorbidities, number of metastatic sites, bone metastasis, and visceral metastasis

## Results




- Pre-publication trend
  - There was no evidence of differential trends between age groups
- Post-publication trend
  - Younger men experienced a more rapid increase in AAP utilization
  - This increase commenced before FDA announced the approval
- Adjusted DID estimates
  - The publication was associated with a 3.5% higher adjusted uptake rate among younger than older men during the first post-publication period (95% CI: 1.2%–5.8%, P = 0.003)
  - This DID estimate reflects nearly three times higher relative to the uptake rate that would have been expected had younger men followed the same trend as older men
  - The estimates plateaued throughout the observed post-publication period

## Conclusions

- Despite the absence of clinical guidance for differential use of AAP to treat mHSPC between age groups, our study found a significantly faster increase in AAP uptake among younger than older men after publication of the pivotal RCTs
- Our study highlights the importance of a future confirmatory study among older men, considering the nonnegligible uncertainties of subgroup analyses in RCTs

## References

1. *Fizazi et al. N Engl J Med. 2017;377(4):352-360. doi:10.1056/NEJMoa1704174*
2. *James et al. New England Journal of Medicine. 2017;377(4):338-351. doi:10.1056/NEJMoa1702900*
3. *Freedland, et al.. Current Medical Research and Opinion. 2021;37(4):609-622.*