Model-free selective inference with conformal p-values

and its application to drug discovery

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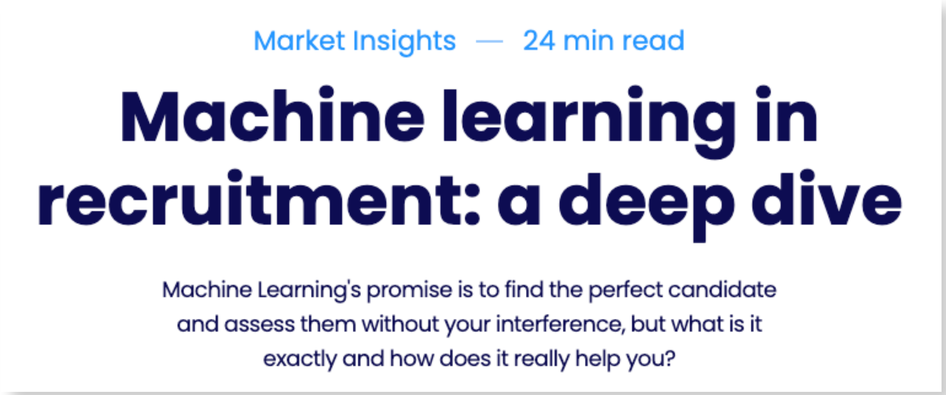
ML prediction assists decision

[VerVoe.com]

[smartdreamers.com]



[HeroHunt.ai]

Job hiring: Who to reach out to?
Who to proceed to interview?

ML prediction assists discovery

[DZone.com]

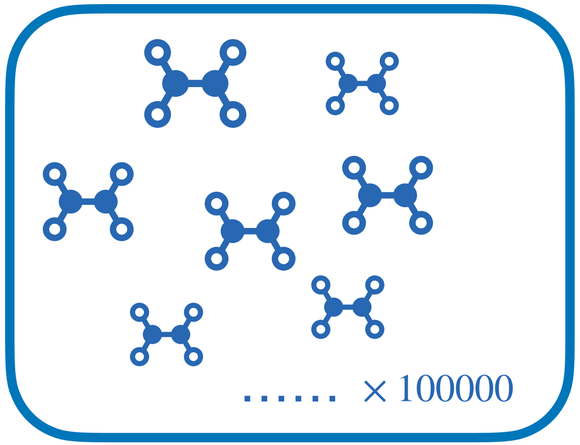
[technologynetworks.com]

Drug discovery: Which molecules/compounds to proceed to physical screening and clinical trials?

Decision and discovery processes

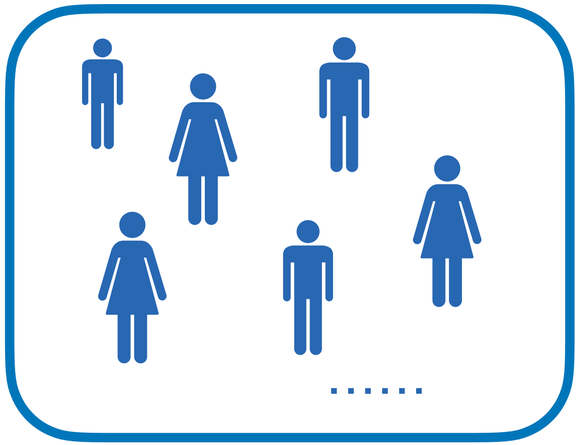
- Find a few interesting cases from a huge pool

Disease (COVID)



Candidate drugs

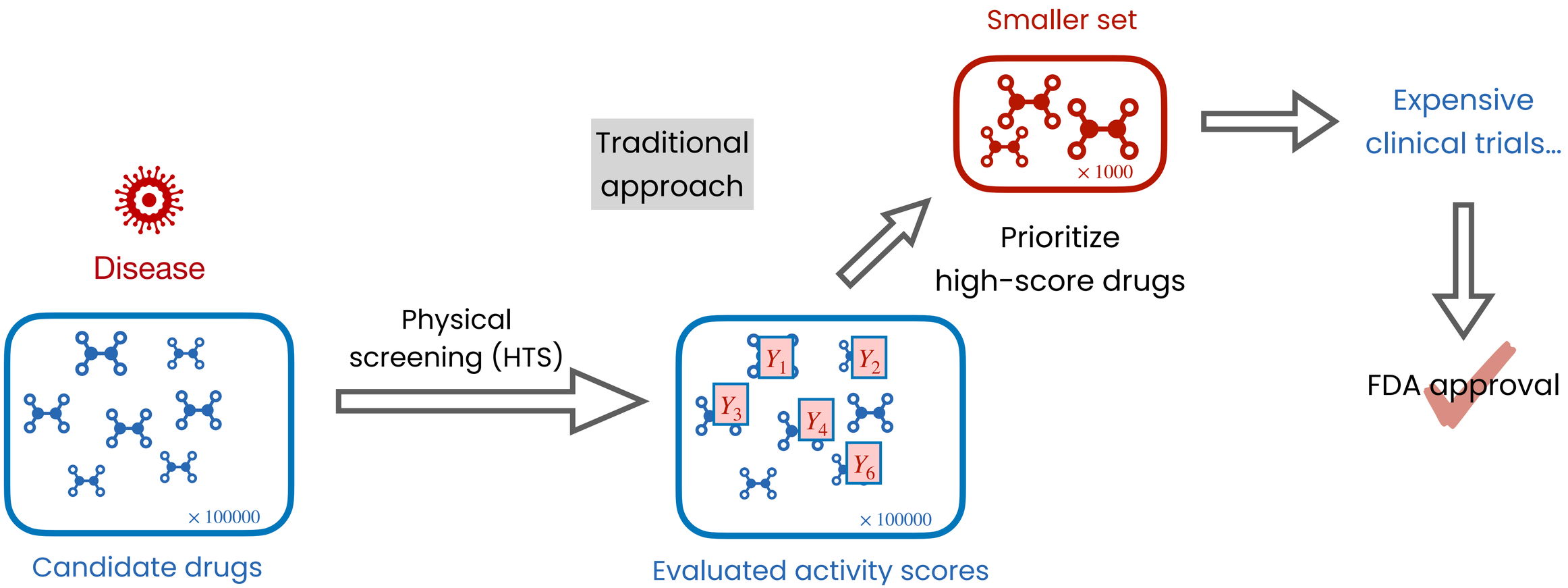
Position



Job applicants

Decision and discovery processes

- Find a few interesting cases from a huge pool



Decision and discovery processes

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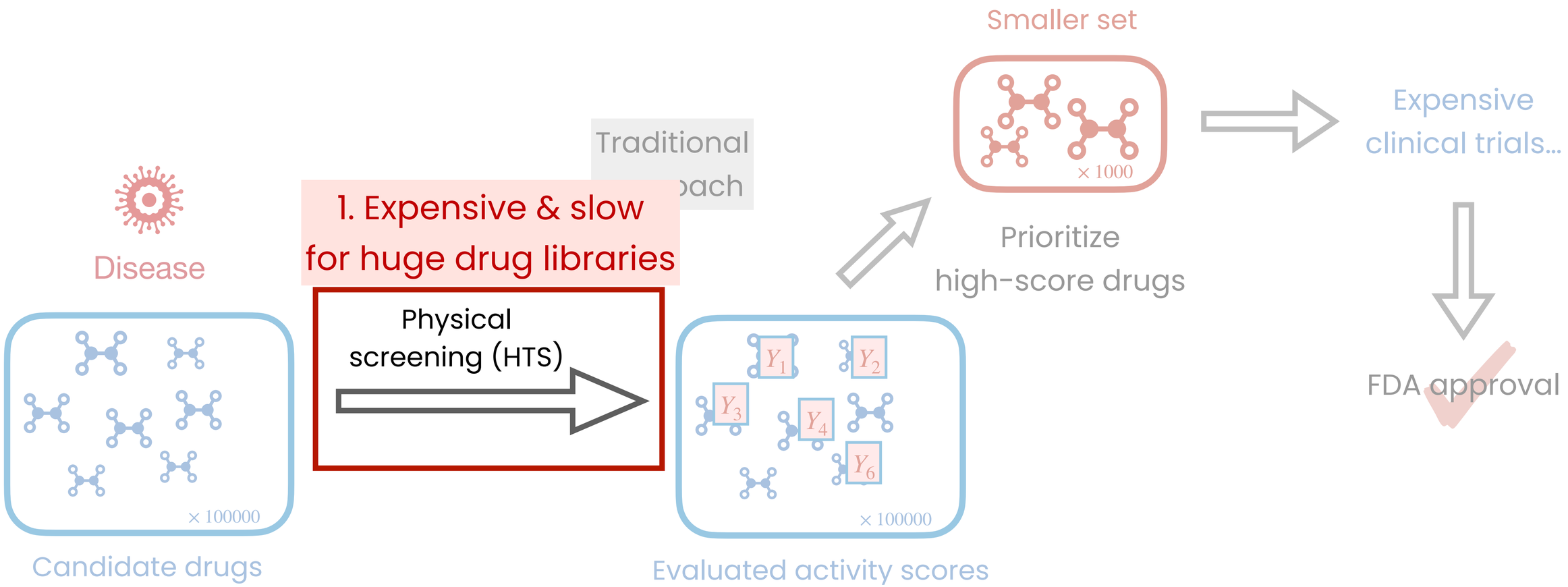

Decision and discovery processes

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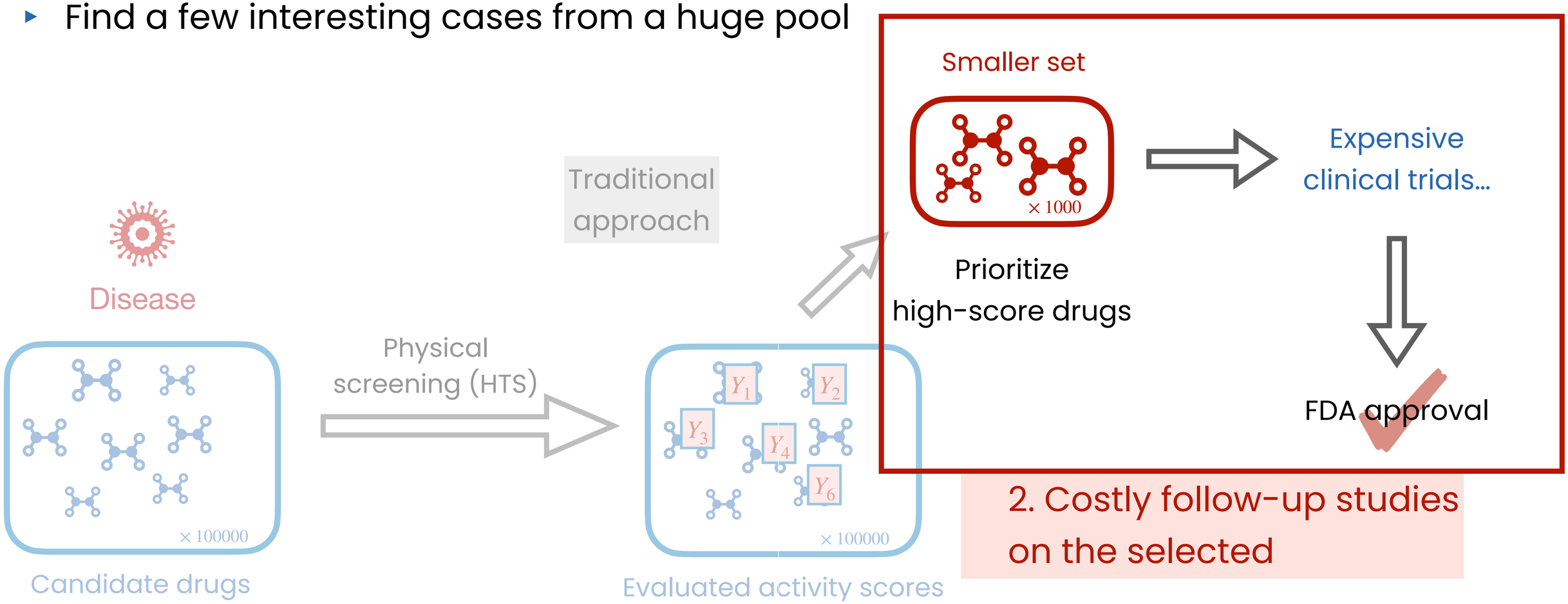
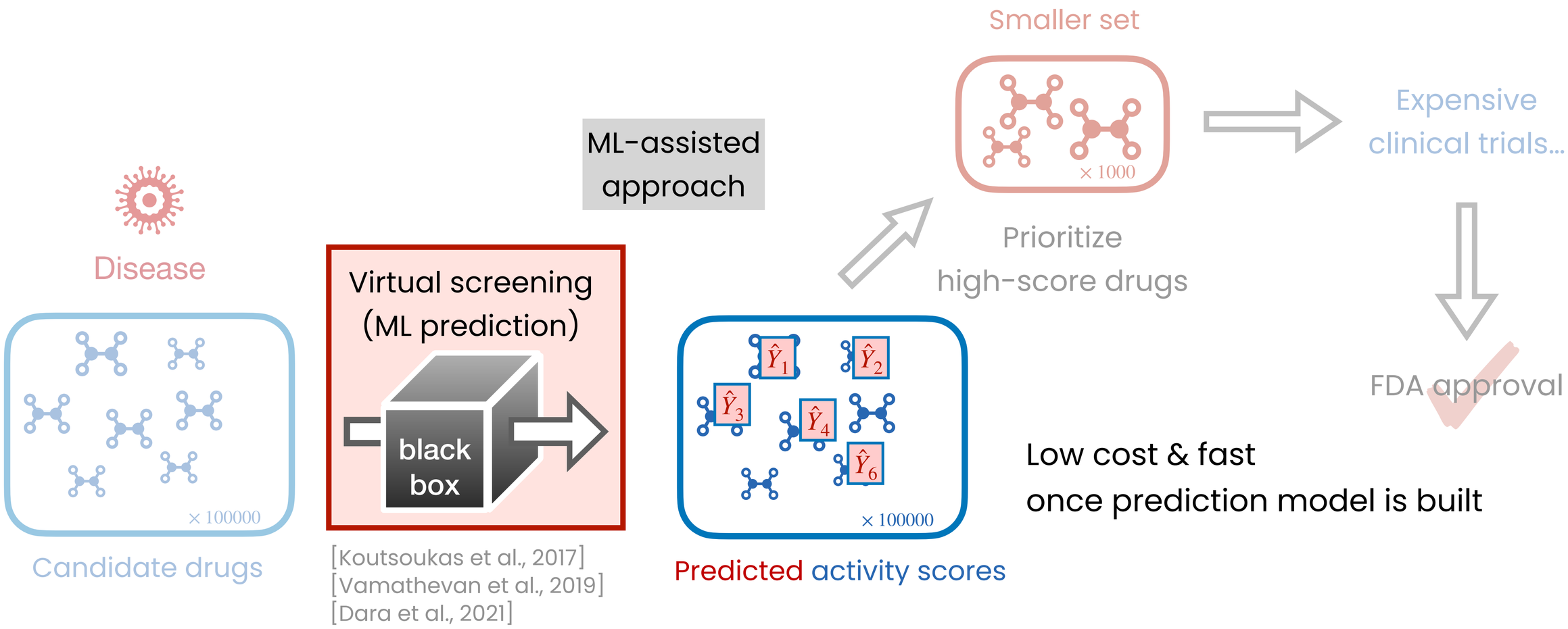


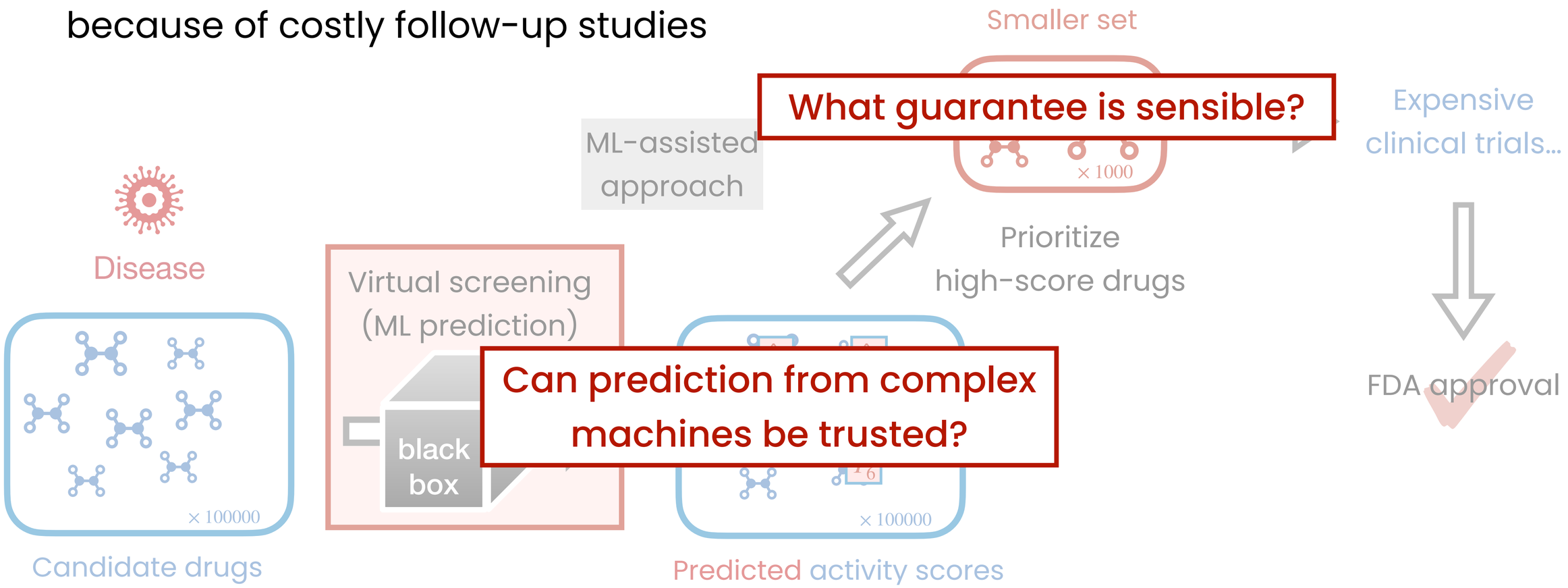
The role of ML in decision and discovery processes

- Find a few interesting cases from a huge pool



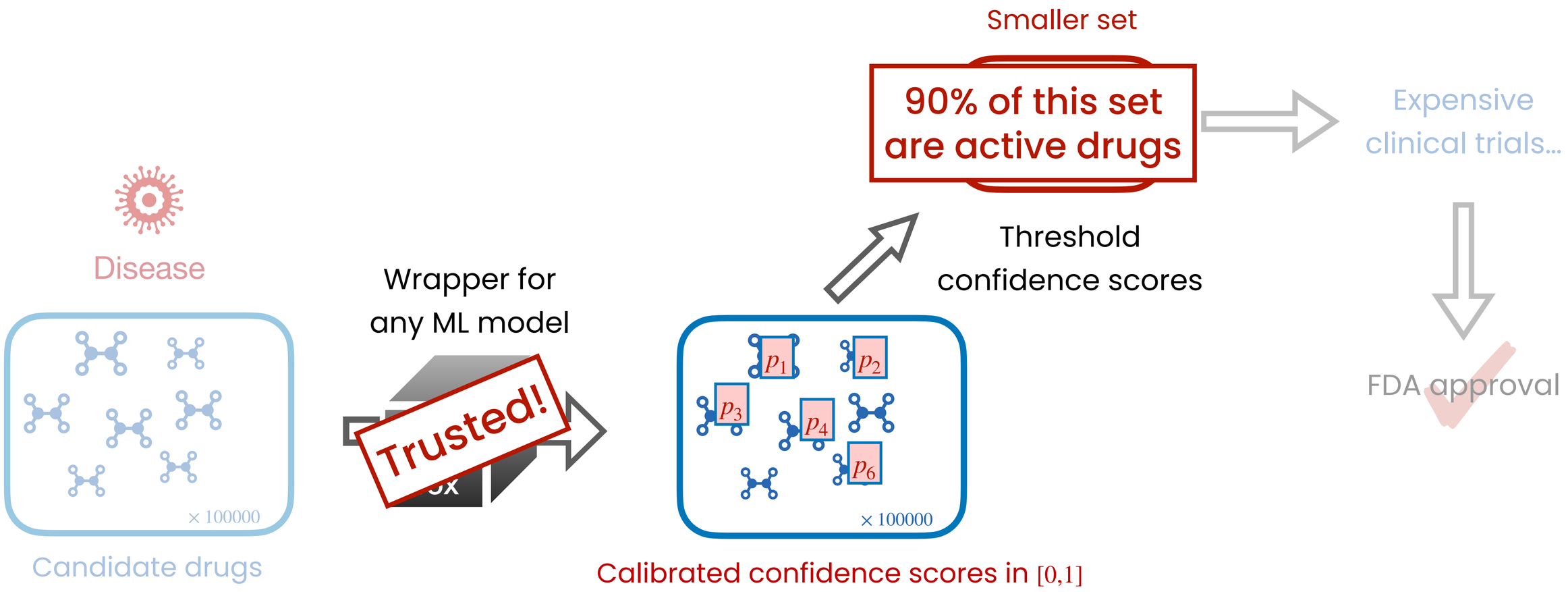
The role of ML in decision and discovery processes

- Error on the selected is concerning because of costly follow-up studies



This work

- Screening with error control on the selected candidates



Mathematical setup

- Any pre-trained ML model $\hat{\mu}: \mathcal{X} \to \mathcal{Y}$
- Training data $\{(X_i, Y_i)\}_{i=1}^{n}$ (already-screened drugs)
- Test samples $\{(X_{n+j}, Y_{n+j})\}_{j=1}^{m}$, only observe covariates $\{X_{n+j}\}_{j=1}^{m}$ (new drugs)
  - $Y \in \{0,1\}$: whether a drug is active for the disease
  - $Y \in \mathbb{R}$: affinity score of a drug for the disease
  - X: physical/chemical structures/properties of the drug

- For now: assume training and test samples are i.i.d. from an unknown distribution
  - Experimentation / Drugs drawn from a diverse drug library
  - Will be relaxed later on to allow for distribution shift

Mathematical setup

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- **Goal**: find large outcomes: $Y_{n+j} > c_{n+j}$ for some user-specified thresholds c_{n+j}
  - c_{n+j}: how active a drug should be to be viewed as “interesting”, a known value

Guarantees we seek for

- Interested in large outcomes: $Y_{n+j} > c_{n+j}$ for some user-specified c_{n+j}

- Our goal is to find a subset $\mathscr{R} \subseteq \{1,\ldots,m\}$ as "promising candidates"
- While controlling the false discovery rate (FDR) below some $q \in (0,1)$

$$FDR = \mathbb{E}[FDP], \quad FDP = \frac{\sum_{j=1}^{m} \mathbf{1}\{j \in \mathscr{R}, Y_{n+j} \leq c_{n+j}\}}{1 \vee |\mathscr{R}|}$$

Number of selected but uninteresting units

≈ Number of selected units

[Benjamini and Hochberg, 1995]

- FDR measures the proportion of follow-up resources wasted on uninteresting cases

Our approach: thresholding confidence measure

- Interested in large outcomes: $Y_{n+j} > c_{n+j}$ for some user-specified c_{n+j}

- Build any monotone score function $V(x, y)$, i.e., $y \le y'$ implies $V(x, y) \le V(x, y')$
  - One-sided residual $V(x, y) = y - \hat{\mu}(x)$
  - Fitted cumulative distribution function $V(x, y) = \hat{\mathbb{P}}(Y \le y \mid X = x)$
- Compute $V_i = V(X_i, Y_i)$ for $i = 1,2,\ldots,n$
- Compute test scores $\hat{V}_{n+j} = V(X_{n+j}, c_{n+j})$ for $j = 1,2,\ldots,m$
- Compute confidence measures (p-value in statistics)

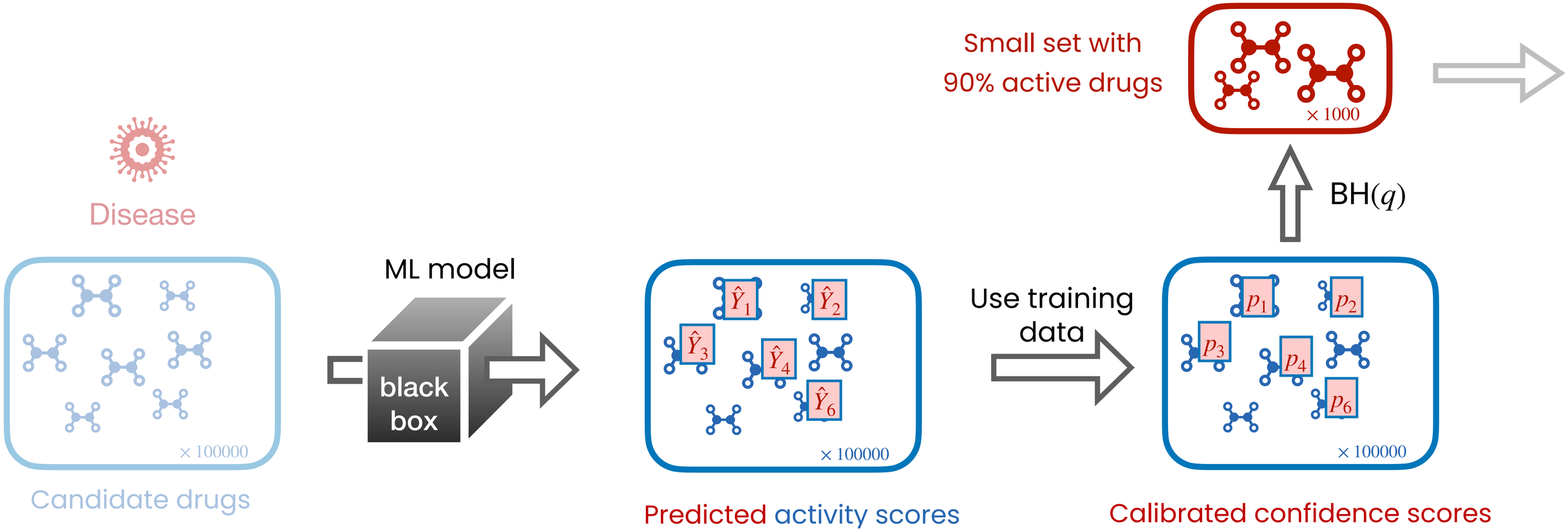
$\approx$ rank of $\hat{V}_{n+j}$ among training scores $\{V_i\}_{i=1}^n$

$$p_j = \frac{\sum_{i=1}^{n} \mathbf{1}\{V_i < \hat{V}_{n+j}\} + U_j}{n+1}, \quad U_j \sim \text{Unif}[0,1]$$

- Get selection set $\mathscr{R}$ by Benjamini-Hochberg procedure applied to $\{p_j\}$ at level q

Our approach: thresholding confidence measure

- Back to the implied pipeline in drug discovery



Interpreting the confidence measure

- Recall: Interested in large outcomes: $Y_{n+j} > c_{n+j}$ for some user-specified c_{n+j}

$$p_j = \frac{\sum_{i=1}^{n} \mathbf{1}\{V_i < \hat{V}_{n+j}\} + U_j}{n+1}, \quad U_j \sim \text{Unif}[0,1]$$

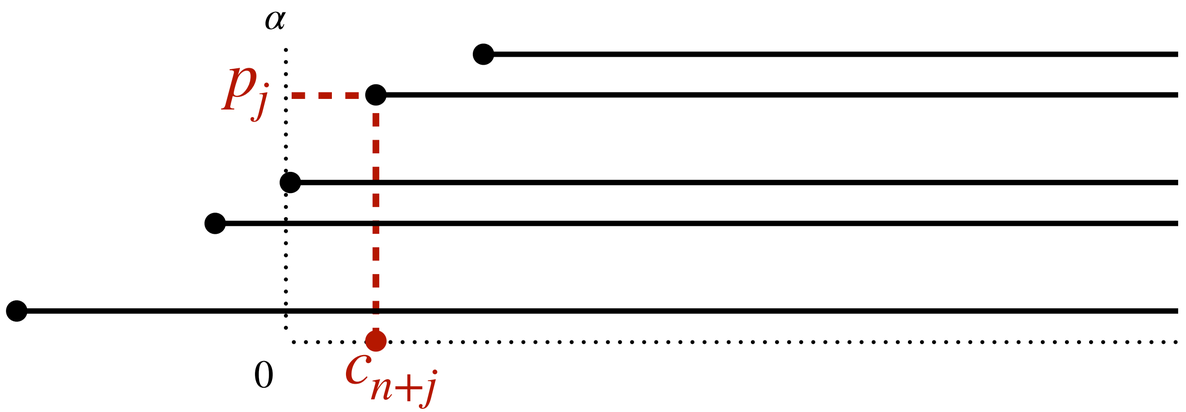
$$p_j \approx \inf\left\{\alpha : c_{n+j} \notin \hat{C}(X_{n+j}; \alpha)\right\}$$

$\hat{C}(X_{n+j}; \alpha)$ is an α-prediction interval for Y_{n+j}, which obeys

$$\mathbb{P}(Y_{n+j} \in \hat{C}(X_{n+j}; \alpha)) \geq 1 - \alpha$$

$\approx$ critical point α such that $\hat{C}(X_{n+j}; \alpha)$ is all larger than c_{n+j}

A smaller p_j means c_{n+j} is smaller than the typical behavior of Y_{n+j}



By monotonicity,

$\hat{C}(X_{n+j}; \alpha) = [\eta(X_{n+j}; \alpha), \infty)$

FDR control with the confidence measure

- Get selection set $\mathscr{R}$ by Benjamini-Hochberg procedure applied to $\{p_j\}$ at level q
  - Set $\mathscr{R} = \{j : p_j \le q\hat{k}/m\}$, where $\hat{k} = \max\left\{k : \sum_{j=1}^{m} \mathbf{1}\{p_j \le qk/m\} \ge k\right\}$

Theorem (J. and Candès, 2022)

If $V(x, y)$ is monotone, the training and test data are i.i.d., and for each j, data in $\{Z_i\}_{i=1}^{n} \cup \{\tilde{Z}_{n+\ell}\}_{\ell \neq j} \cup \{Z_{n+j}\}$ are mutually independent for $Z_i = (X_i, Y_i)$ and $\tilde{Z}_{n+j} = (X_{n+j}, c_{n+j})$, Then for any $q \in (0,1)$, the output $\mathscr{R}$ at level q obeys $FDR \le q$.

- True for random c_{n+j} (will my health risk tomorrow be higher than today?)

Power boosting

- While FDR is controlled for any monotone score $V(x, y)$, some makes it powerful
- If the thresholds are constant $c_{n+j} \equiv c$, a particularly powerful choice is `clipped' score

$$V(x, y) = +\infty \cdot \mathbf{1}\{y > c\} + c \cdot \mathbf{1}\{y \leq c\} - \hat{\mu}(x)$$

- In binary case and $c = 0$, the ideal score is monotone in $\mathbb{P}(Y = 1 \mid X = x)$ (see paper)

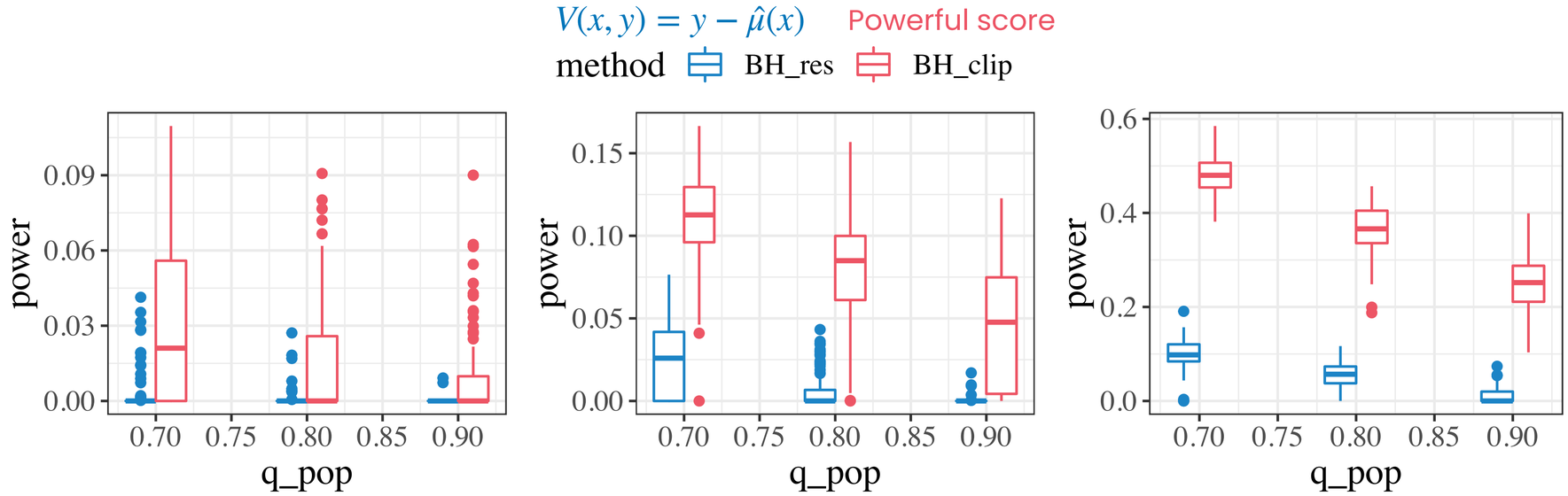
Real application: drug property prediction for HIV

- Binary $Y \in \{0,1\}$: whether the drug interacts with the disease
- The drug library is $n_{tot} = 41127$ in total, use $6:2:2$ split
- Very sparse data: only 3% drugs are active
- Our hope: find a smaller subset to proceed so that $(1-q)$ of the subset are active drugs
- FDR level $q \in \{0.1,0.2,0.5\}$, use a small neural network (can be more complicated)

	Realized FDR			**Power**			$\lvert\mathscr{R}\rvert$		
FDR level	0.1	0.2	0.5	0.1	0.2	0.5	0.1	0.2	0.5
Powerful score	**0.0957**	**0.196**	**0.495**	0.0788	0.174	0.410	26.5	64.2	240
Score $V(x,y) = y - \hat{\mu}(x)$	**0.0989**	**0.196**	**0.494**	0.0766	0.174	0.410	25.8	64.4	239

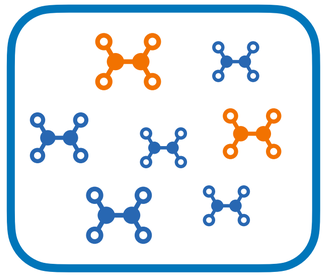
Real application: drug-target-interaction prediction

- Davis dataset, $Y \in \mathbb{R}$ continuous binding affinities, X feature for a drug-target pair
- The drug library is $n_{tot} = 30060$ in total, use $2:2:6$ split
- Set c_{n+j} as the q_{pop}-th quantile of the outcomes in the first training fold with the same binding target as test sample j, where $q_{pop} \in \{0.7, 0.8, 0.9\}$
- FDR level $q \in \{0.1, 0.2, 0.5\}$

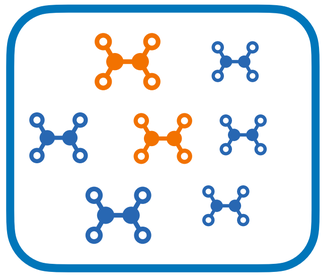


Distribution shifts

- The only assumption for this method to work is i.i.d. data
- Are my evaluated drugs comparable to the unknown drugs?
  - **Yes** if the evaluated ones are drawn without preference from your library



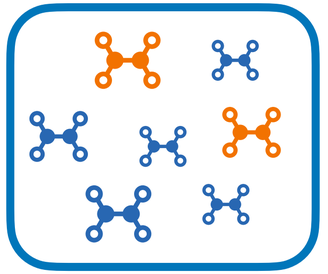
Training drugs



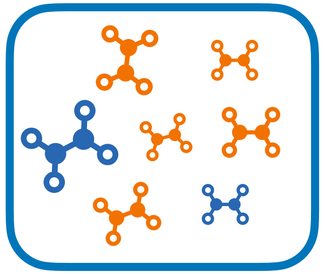
New drugs

Distribution shifts

- The only assumption for this method to work is i.i.d. data
- Are my evaluated drugs comparable to the unknown drugs?
  - **Yes** if the evaluated ones are drawn without preference from your library
  - **No** if you preferred drugs with some specific structures, etc



Training drugs



New drugs

- Similar issues happen in job hiring, health monitoring…
  - Candidates documented last year may differ from current
  - Patients may differ in demographics across hospitals
  - People under treatment may be different than those under control
- Forthcoming: A new procedure **exactly** controlling FDR under covariate shift

Summary

- In prediction-assisted screening problems, FDR can be a sensible measure
- A method that turns any prediction model into a reliable selection procedure
  - Useful if interested in “large” outcomes
  - Builds confidence scores (p-values) upon any prediction model
  - Controls FDR so that your follow-up investigations are well-deserved
- Extension to situations with covariate shifts
  - Some more complicated methodology & theory

arXiv: 2210.01408