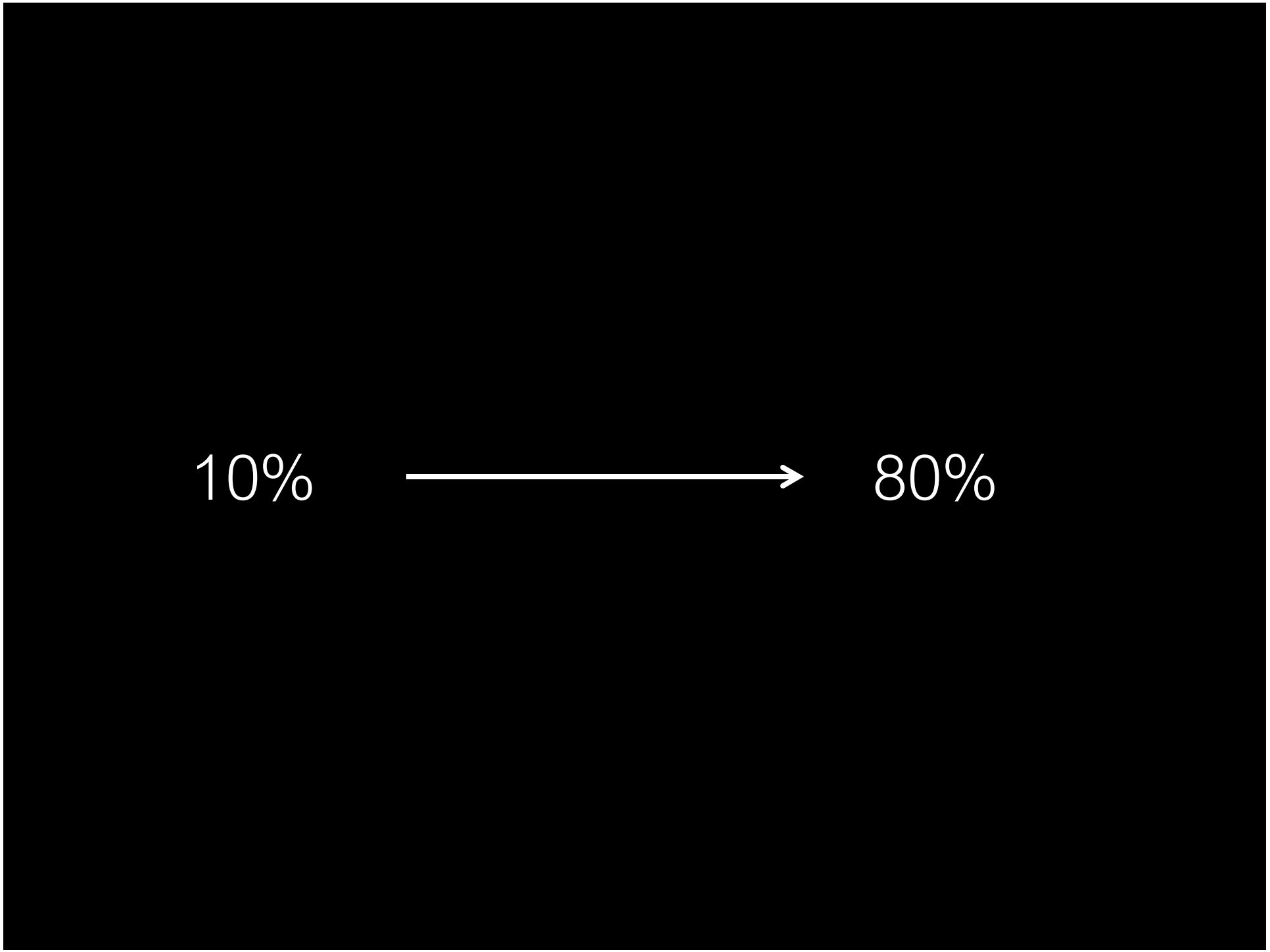
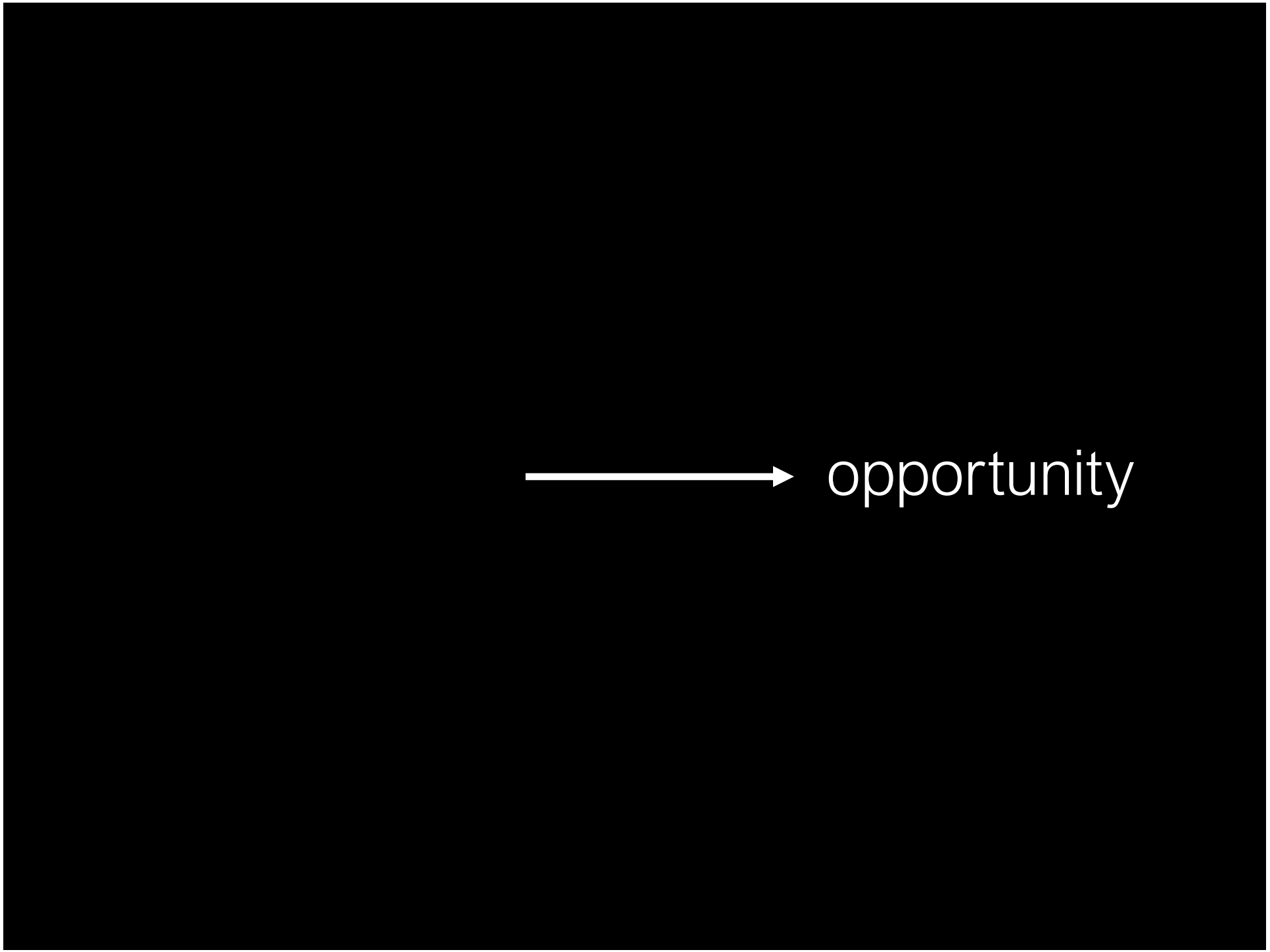
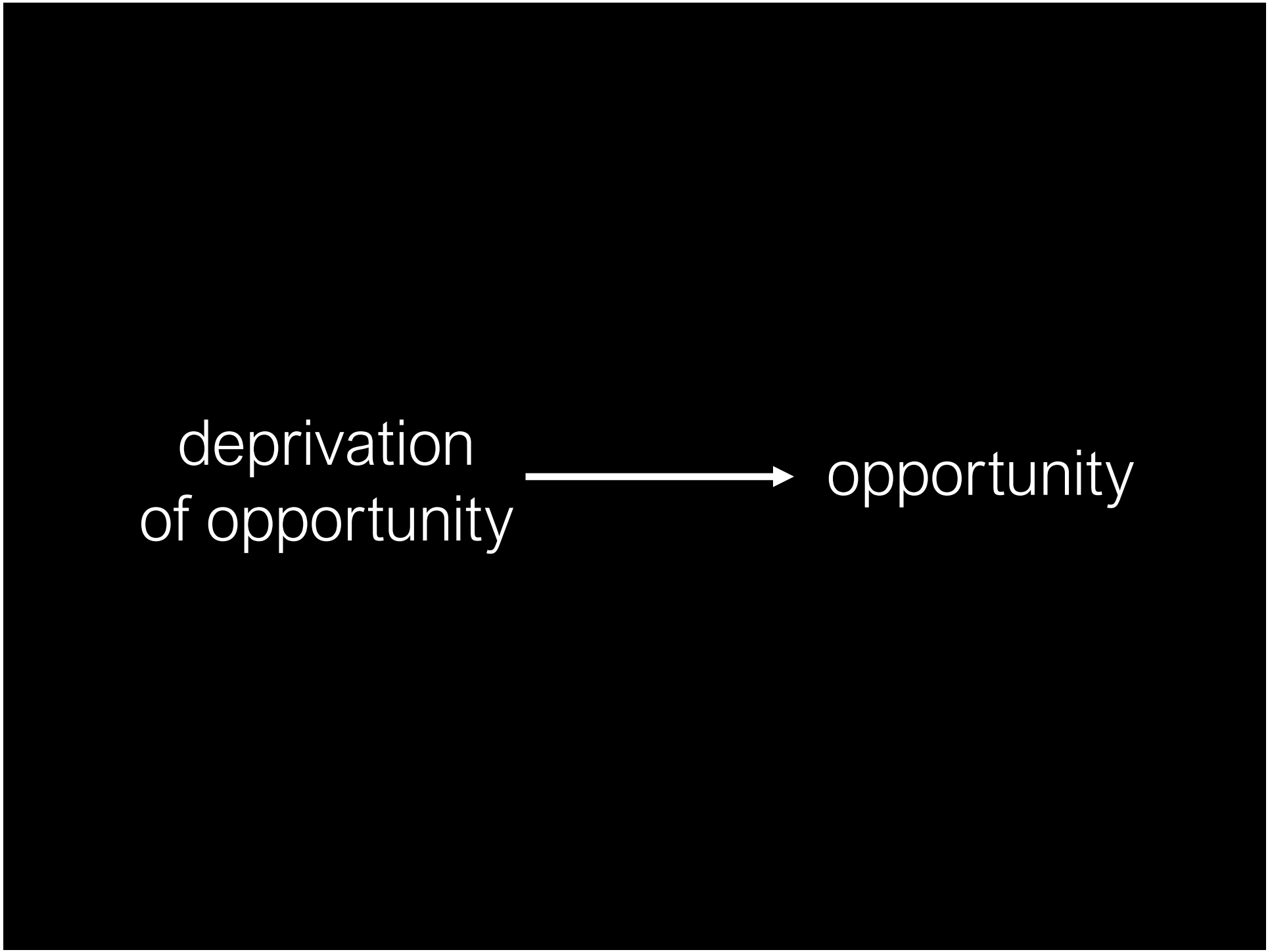
A Catalog of Moral Inefficiencies in Drug Development: The Trajectory

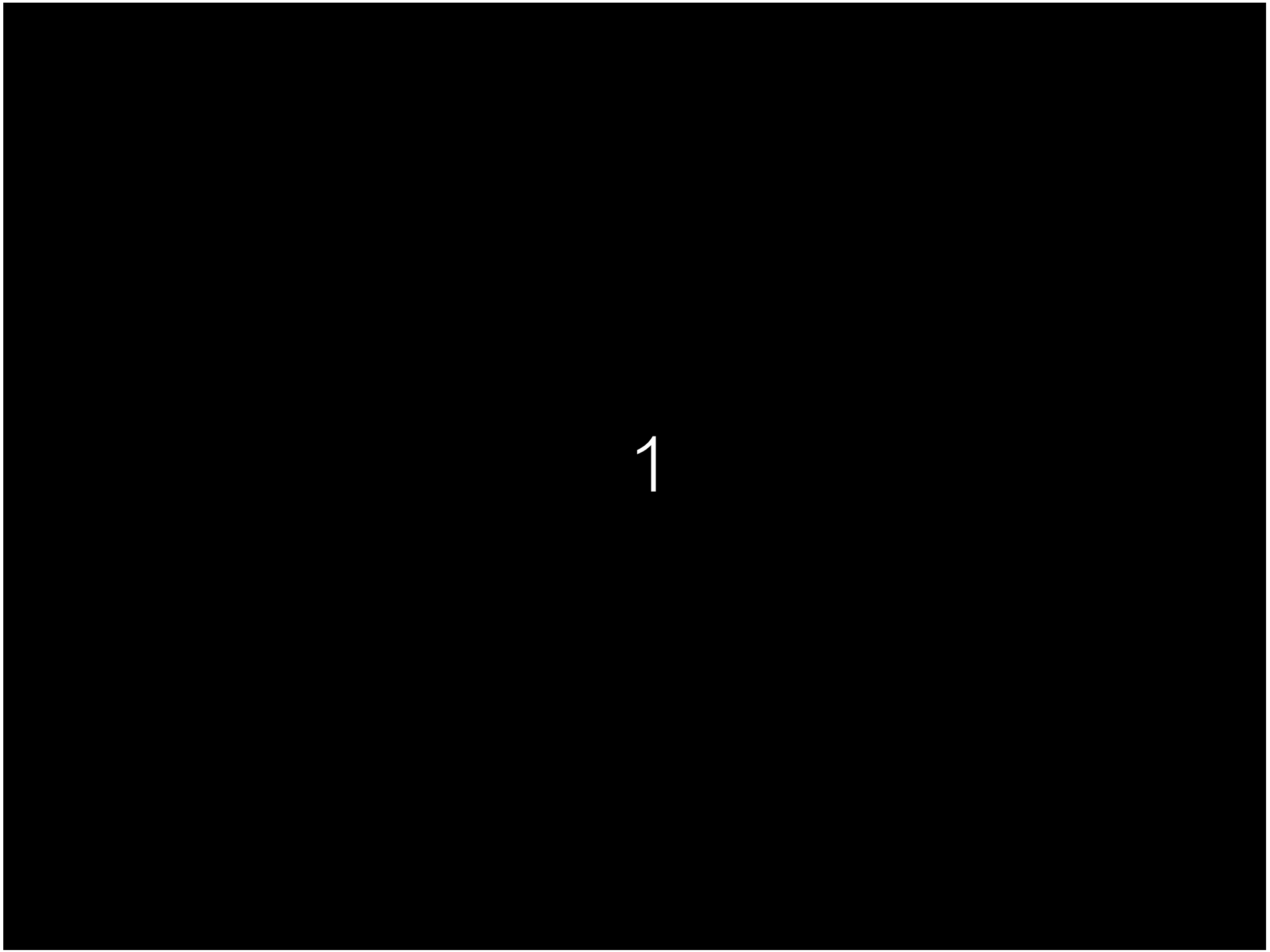
Jonathan Kimmelman
Dept Equity, Ethics and Policy • McGill University

Source: Wikipedia


10%
80%

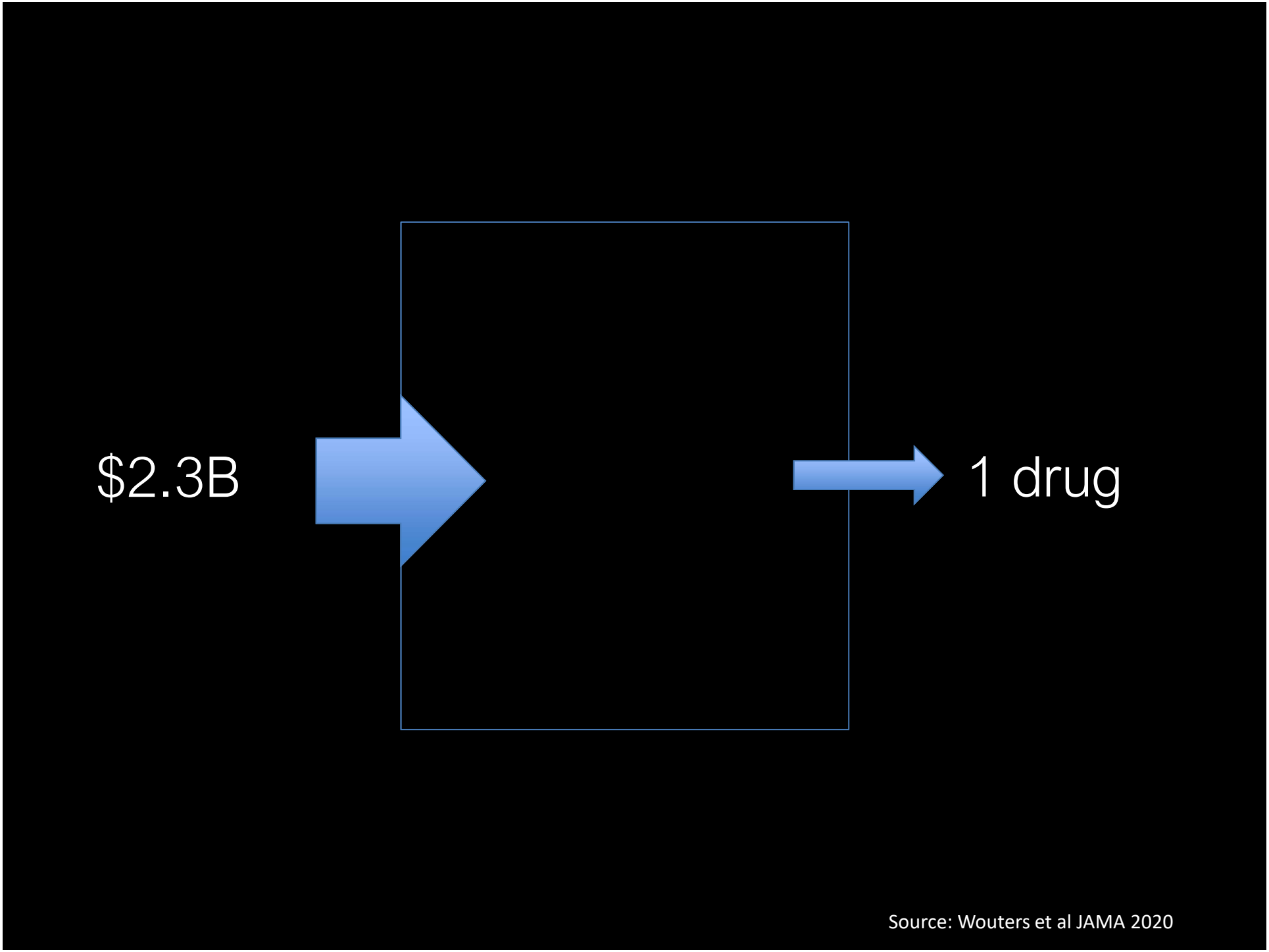

opportunity


deprivation
of opportunity
opportunity

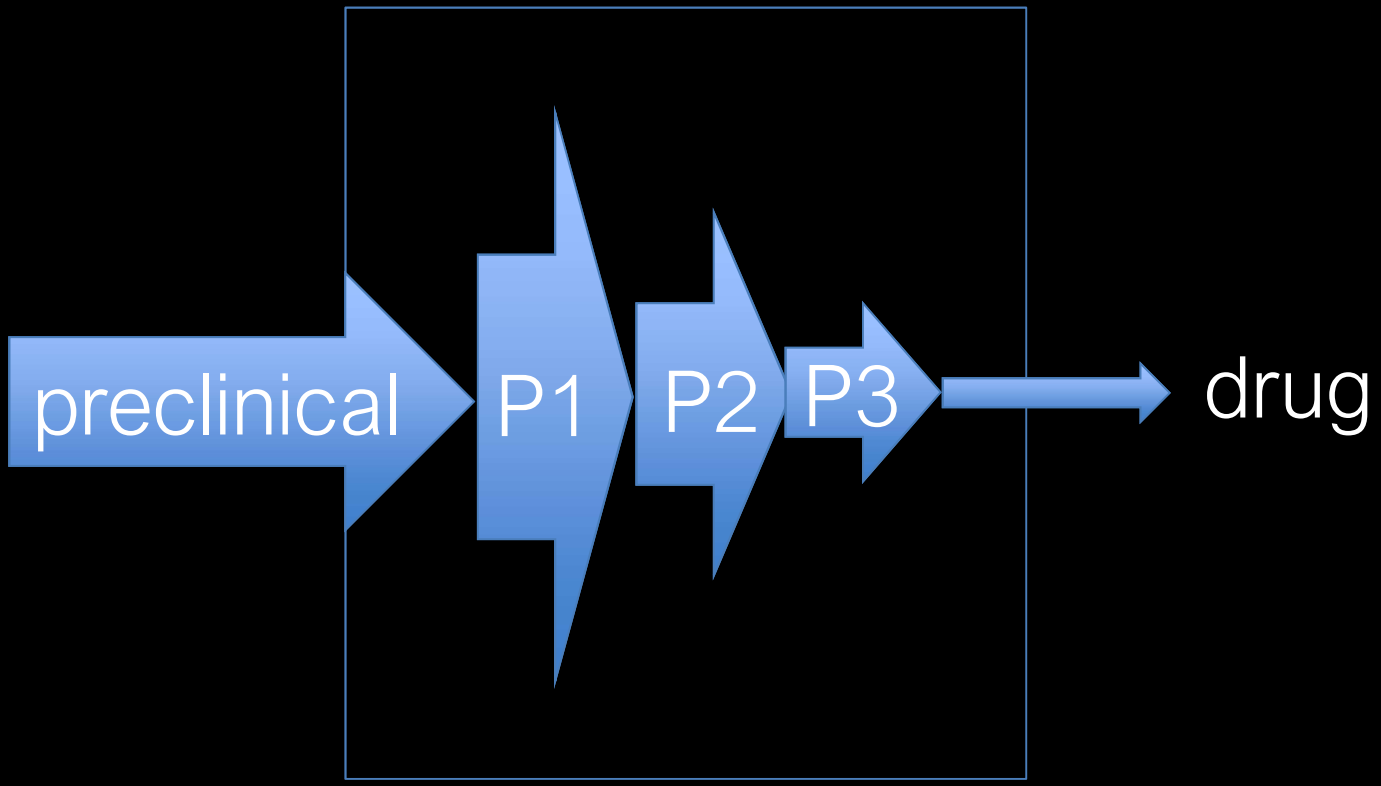

1

maximize moral efficiency

1. moral efficiency



Source: Wouters et al JAMA 2020

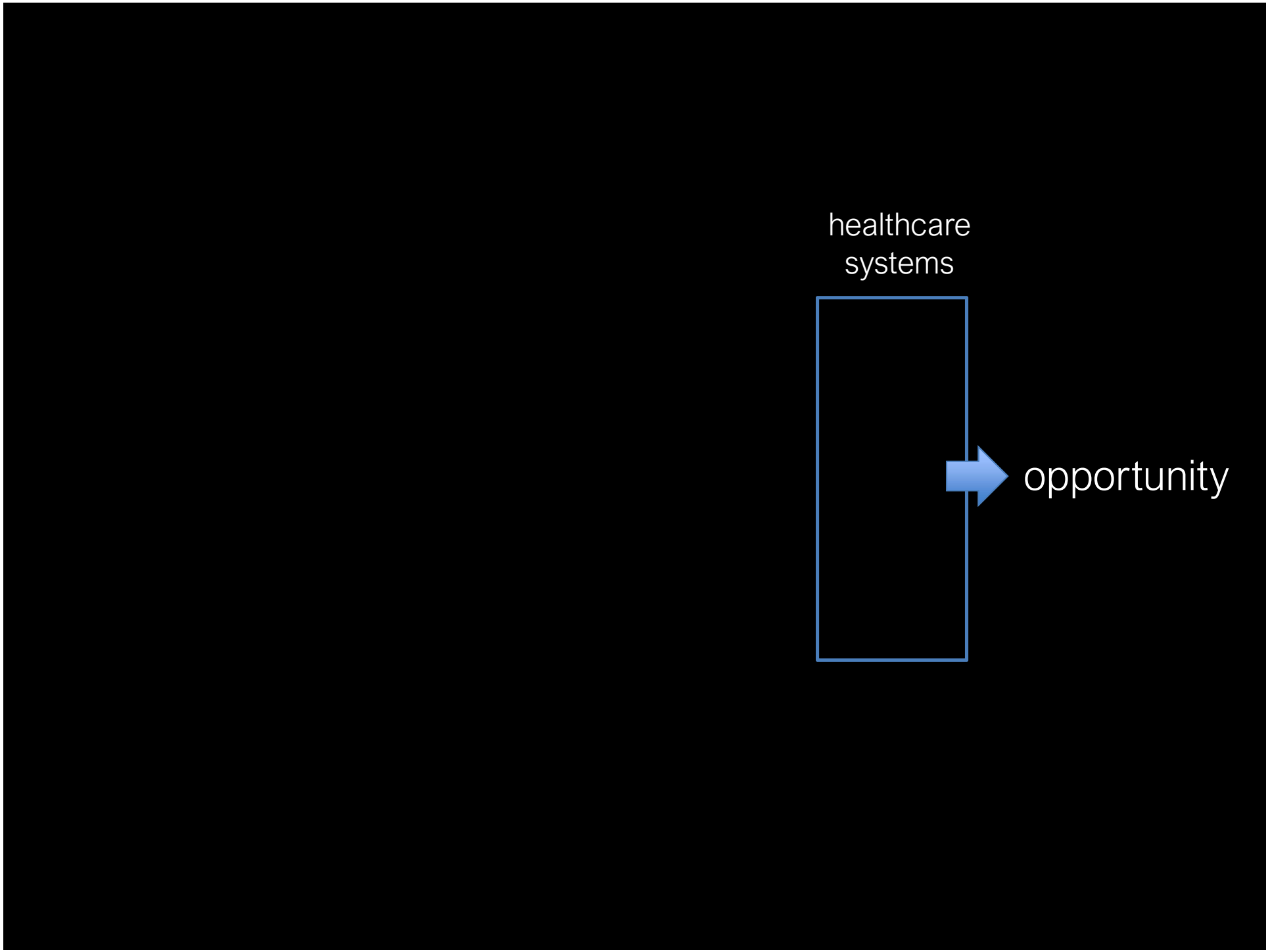

preclinical
P1
P2
P3
drug

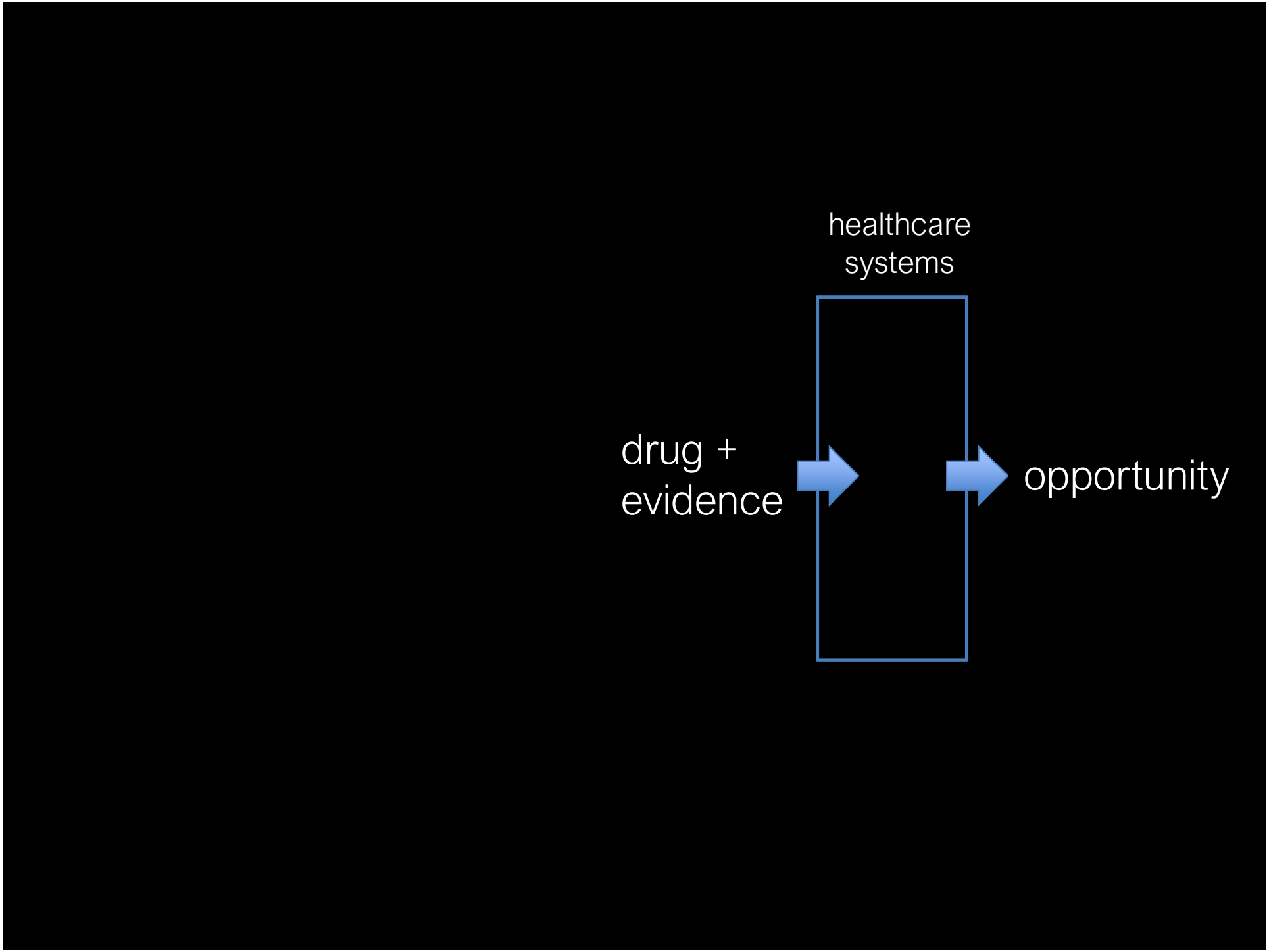

ZONE B
12 SAINT-JÉRÔME
SRB PIE-IX
MASCOUCHE 15
N
1 HONORÉ-BEAUGRAND
Radisson
Langelier
Cadillac
Assomption
Viau
Pie-IX
Joliette
Préfontaine
Frontenac
Papineau
Beaudry
4 LONGUEUIL–UNIVERSITÉ-DE-SHERBROOKE
Jean-Drapeau
2 MONTMORENCY
De la Concorde
Cartier
Henri-Bourassa
SAINT-MICHEL
D'Iberville
Sauvé
Crémazie
Jarry
Fabre
Jean-Talon
Beaubien
Rosemont
Laurier
Mont-Royal
Sherbrooke
4
BERRI-UQAM
5
DEUX-MONTAGNES A4
ANSE-À-L'ORME A3
YUL-AÉROPORT-MONTRÉAL-TRUDEAU A2
ZONE A
Parc
De Castelnau
Acadie
Outremont
Édouard-Montpetit
Université-de-Montréal
Côte-des-Neiges
Saint-Laurent
Place-des-Arts
McGill
Peel
Guy-Concordia
Atwater
GARE CENTRALE
Champ-de-Mars
Place-d'Armes
Square-Victoria–OACI
Bonaventure
MONT-SAINT-HILAIRE 13
2 CÔTE-VERTU
Du Collège
De la Savane
Namur
Plamondon
Côte-Sainte-Catherine
SNOWDON
11 VAUDREUIL/HUDSON
Villa-Maria
Vendôme
Lucien-L'Allier
Georges-Vanier
Lionel-Groulx
Charlevoix
Place-Saint-Henri
747 YUL AÉROPORT MONTRÉAL-TRUDEAU
LaSalle
1 ANGRIGNON
Monk
Jolicoeur
Verdun
De l'Église
14 CANDIAC
ZONE B
A1 BROSSARD
RÉSEAUX
Métro
1 Ligne verte
2 Ligne orange
4 Ligne jaune
5 Ligne bleue
Train
11 Ligne Vaudreuil/Hudson
12 Ligne Saint-Jérôme
13 Ligne Mont-Saint-Hilaire
14 Ligne Candiac
15 Ligne Mascouche
REM
A Ligne A
A1 Brossard
A2 YUL-Aéroport-Montréal-Trudeau
A3 Anse-à-l'Orme
A4 Deux-Montagnes
LÉGENDE
SRB Service rapide bus
Train interurbain · VIA Rail · Amtrak
Bus interurbain Gare d'autocars de Montréal
Stationnement
YUL Aéroport Montréal-Trudeau
Ascenseur
Ascenseur Ligne 2 - Orange Ligne 1 - Verte
Correspondance
Ligne projetée
ZONES TARIFAIRES
A Agglomération de Montréal
B Agglomération de Longueuil et Laval

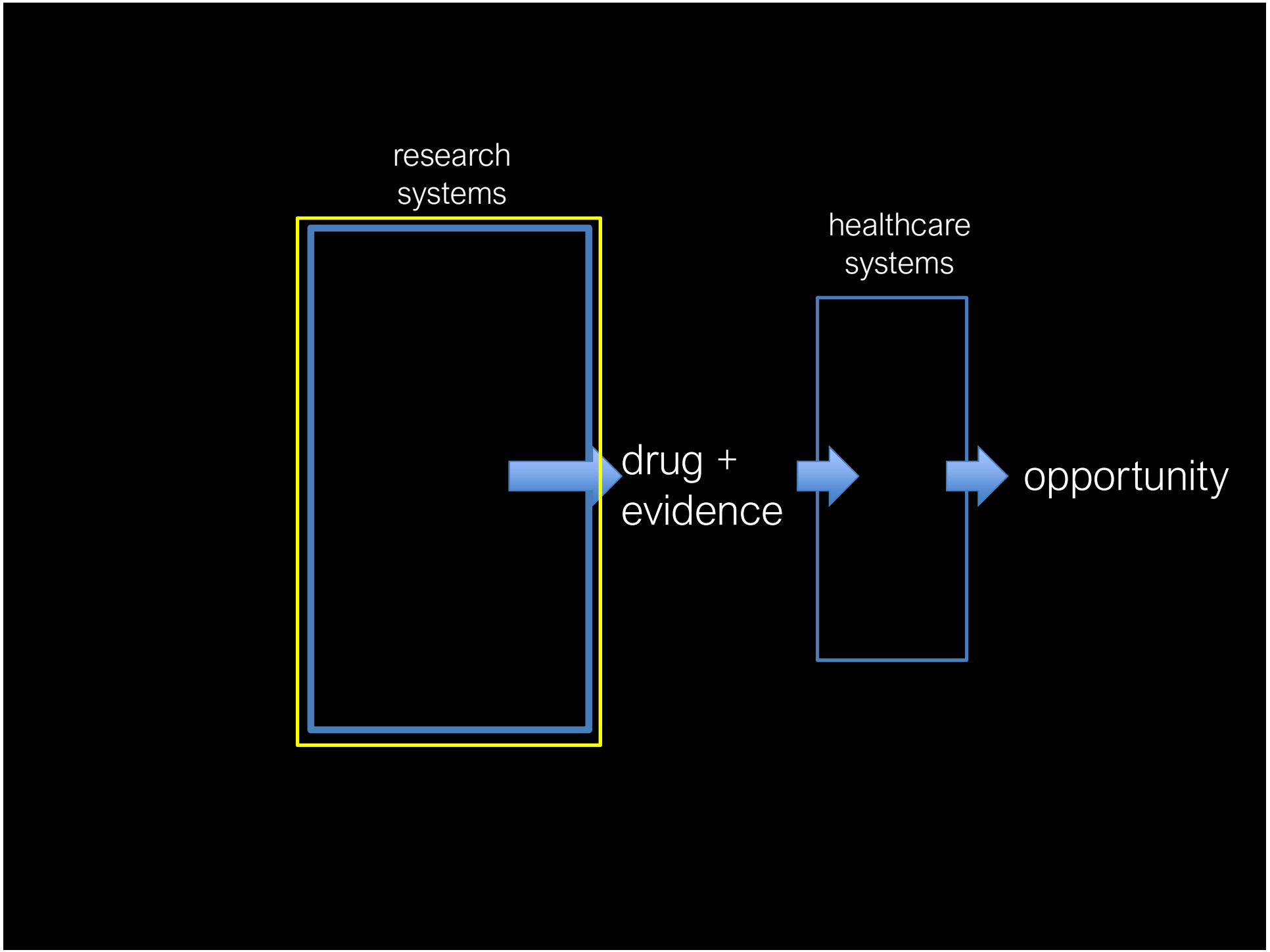
1) focuses on the material
(not moral)

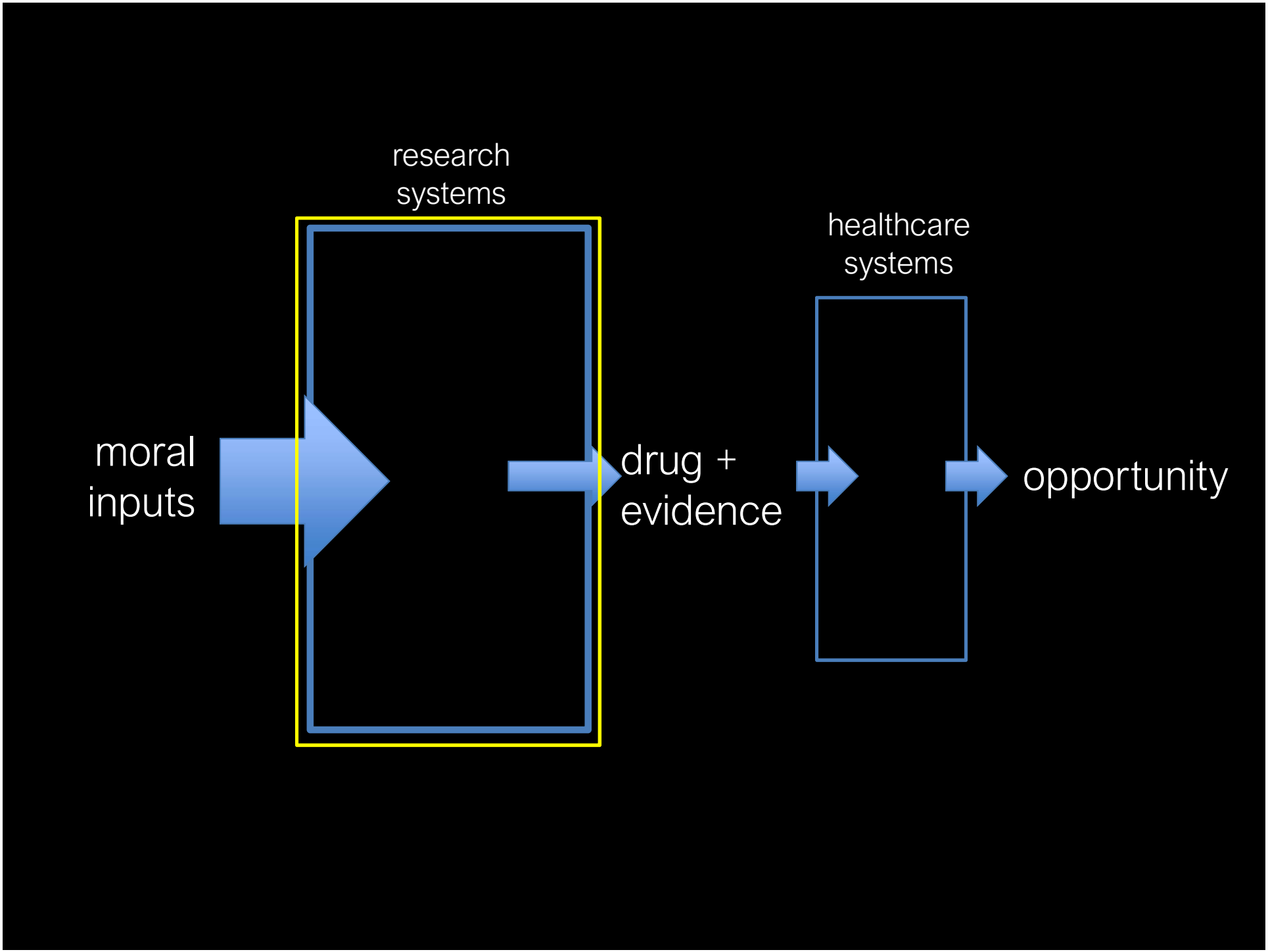
2) stunted model of the science

3) encourages the wrong policies


healthcare
systems
opportunity


healthcare
systems
drug +
evidence
opportunity


research
systems
healthcare
systems
drug +
evidence
opportunity


research
systems
healthcare
systems
moral
inputs
drug +
evidence
opportunity

5

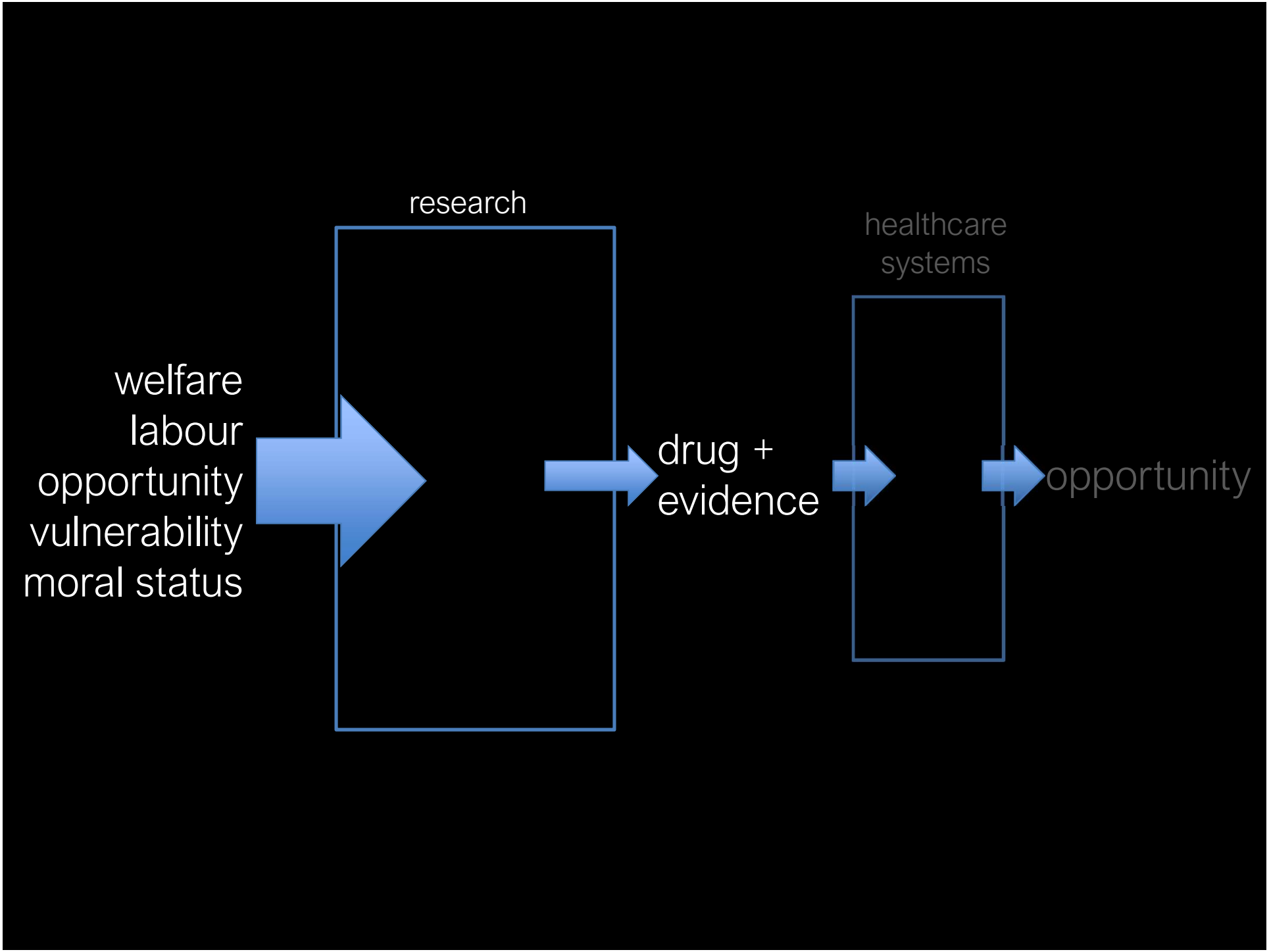
i) welfare

ii) labour

iii) opportunity cost

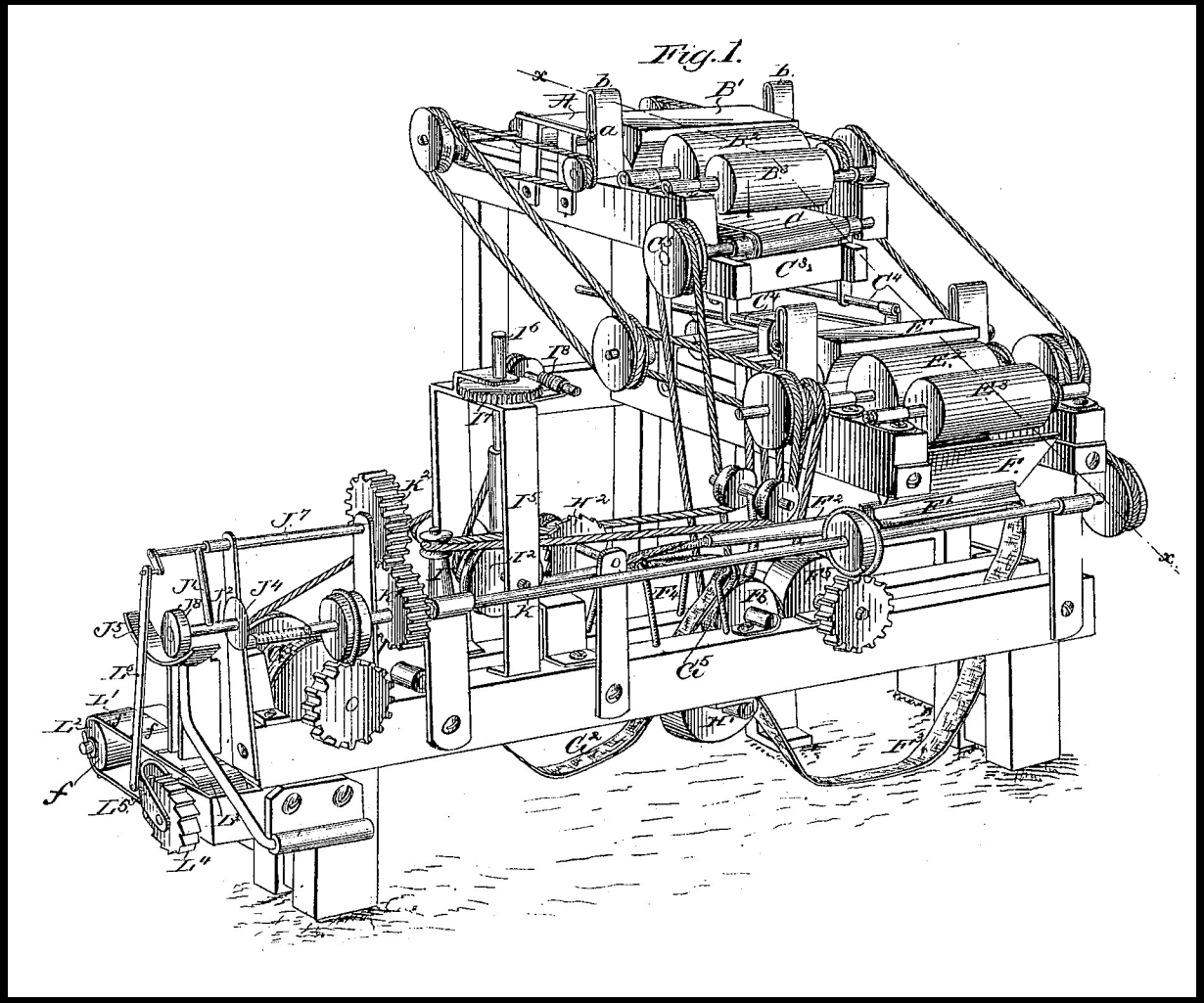
vi) vulnerability

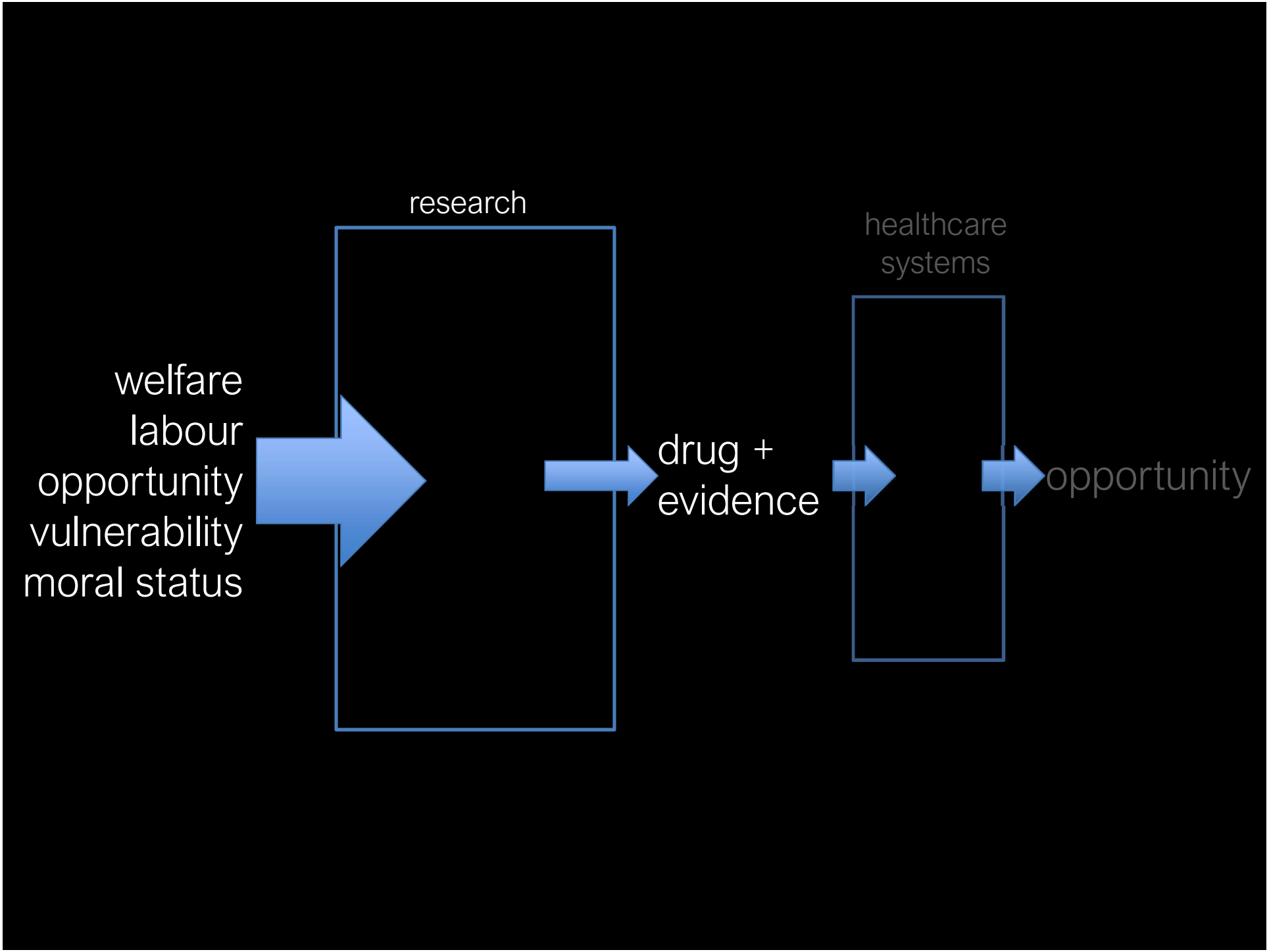
v) moral status


research
healthcare systems
welfare
labour
opportunity
vulnerability
moral status
drug +
evidence
opportunity

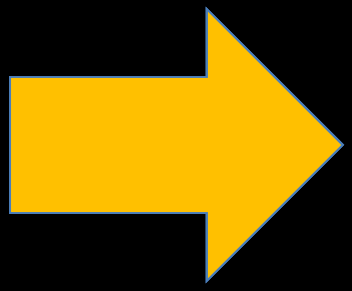
2. moral machinery

Fig. 1.



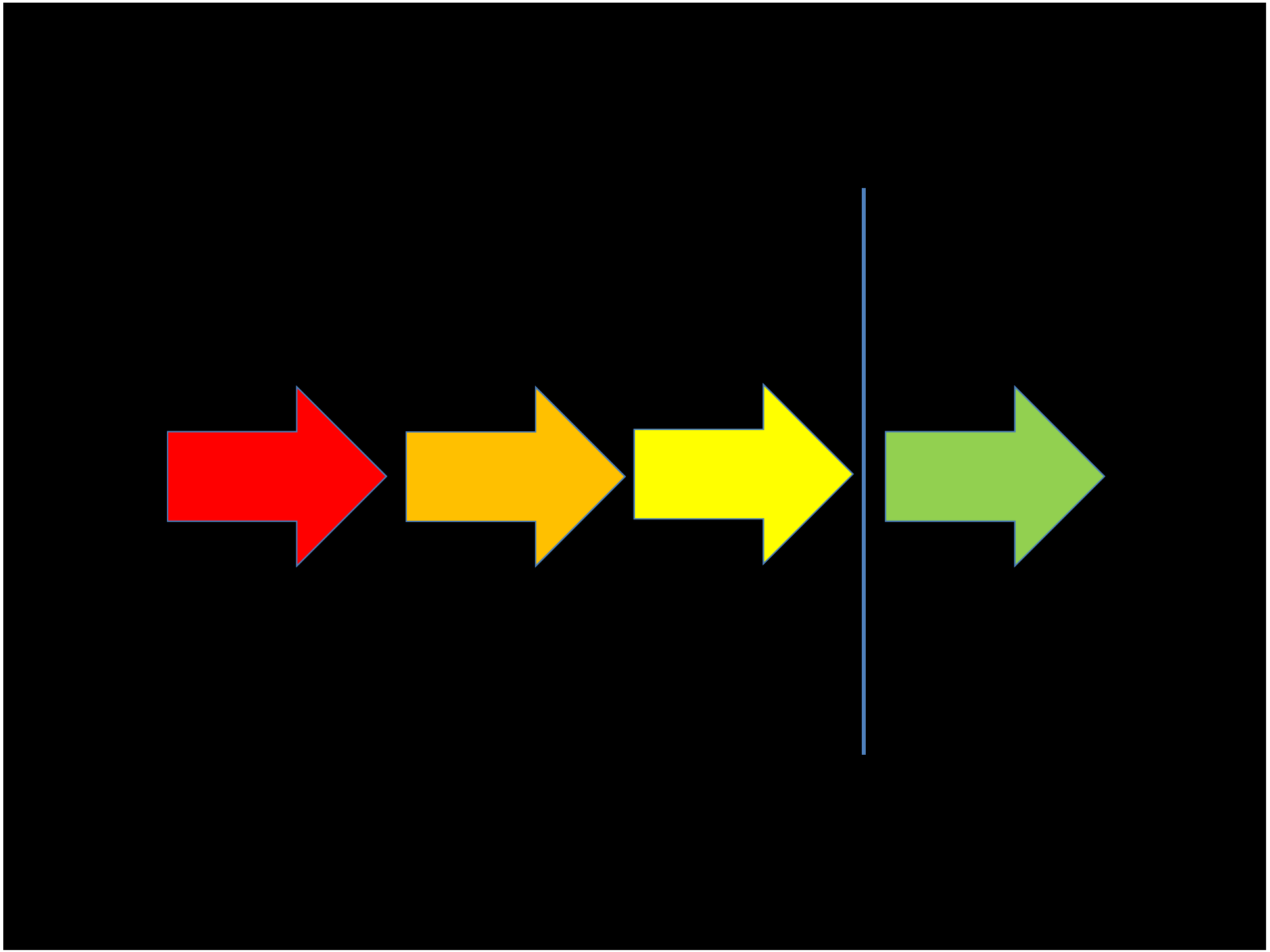

research
healthcare systems
welfare
labour
opportunity
vulnerability
moral status
drug +
evidence
opportunity

i) studies



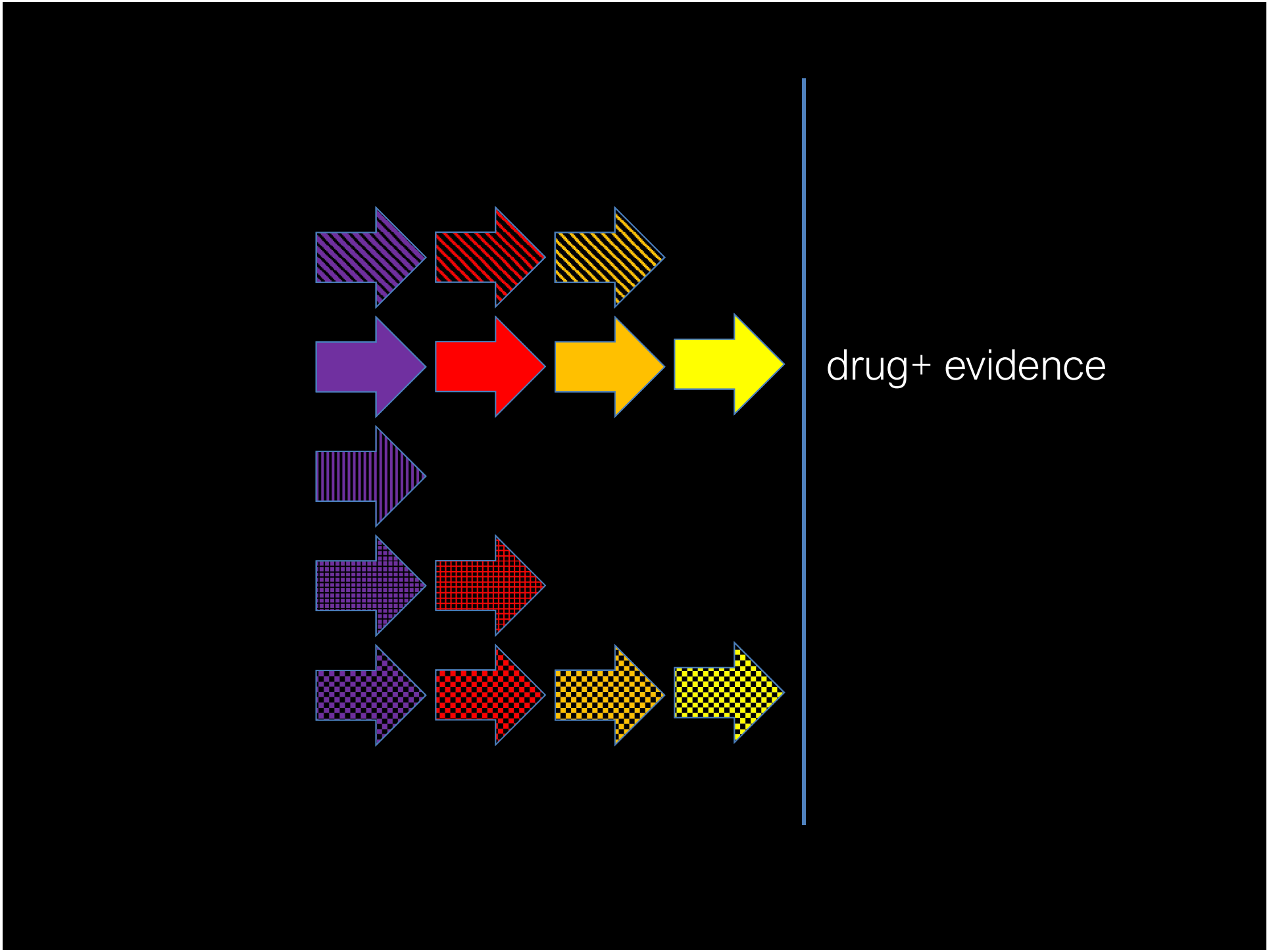
decision device

ii) trajectories

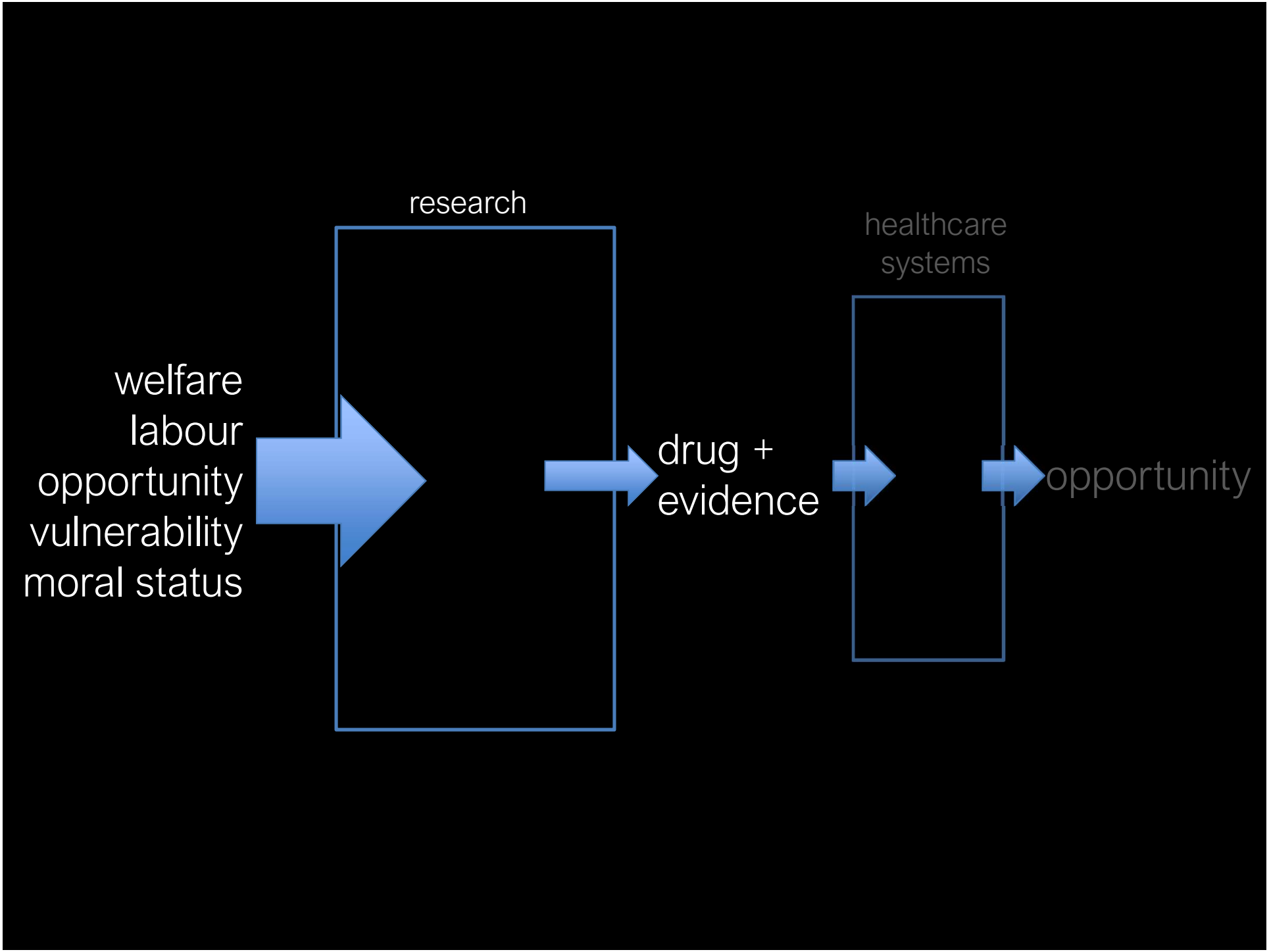


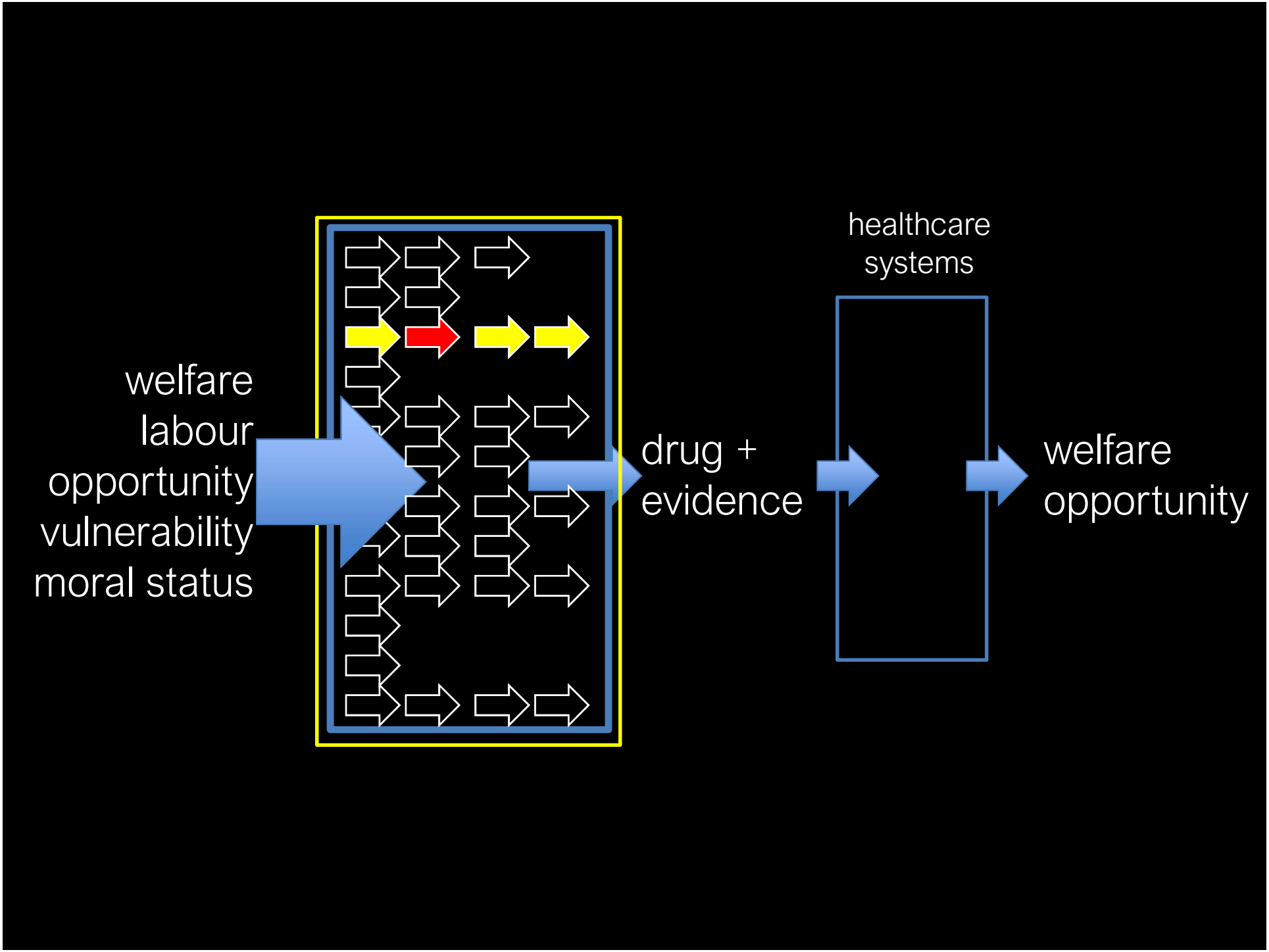
resolve uncertainty about value of a strategy

iii) programs

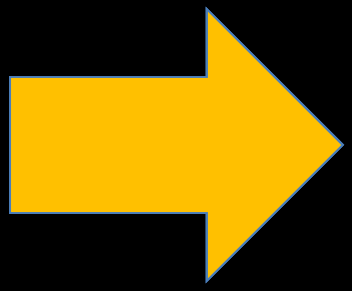

drug+ evidence

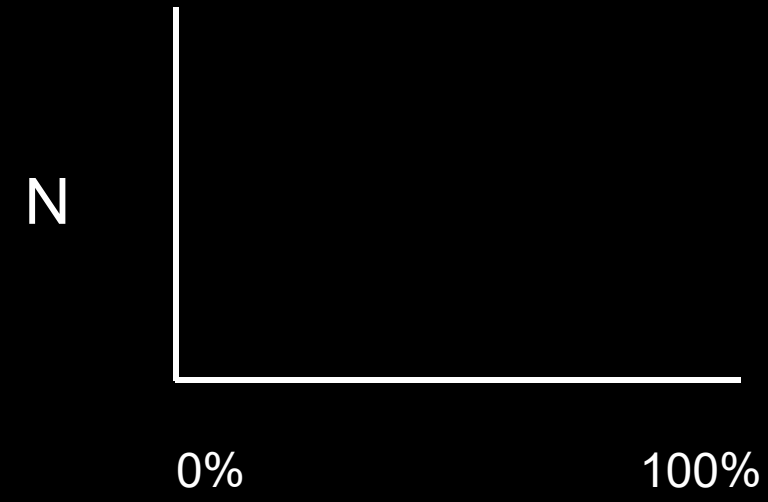
discover ≥ 1 effective strategy


research
healthcare systems
welfare
labour
opportunity
vulnerability
moral status
drug +
evidence
opportunity


welfare
labour
opportunity
vulnerability
moral status
drug +
evidence
healthcare
systems
welfare
opportunity

3. theory of experiments

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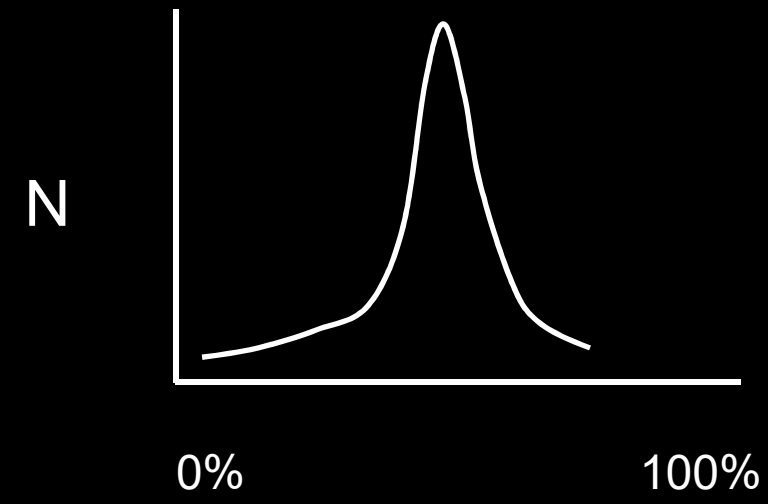
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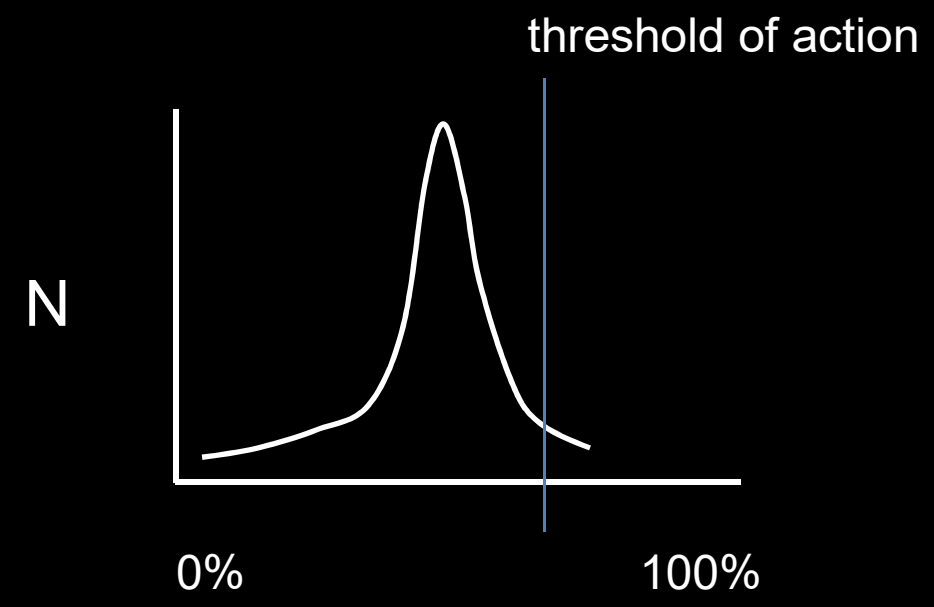
threshold of action
N
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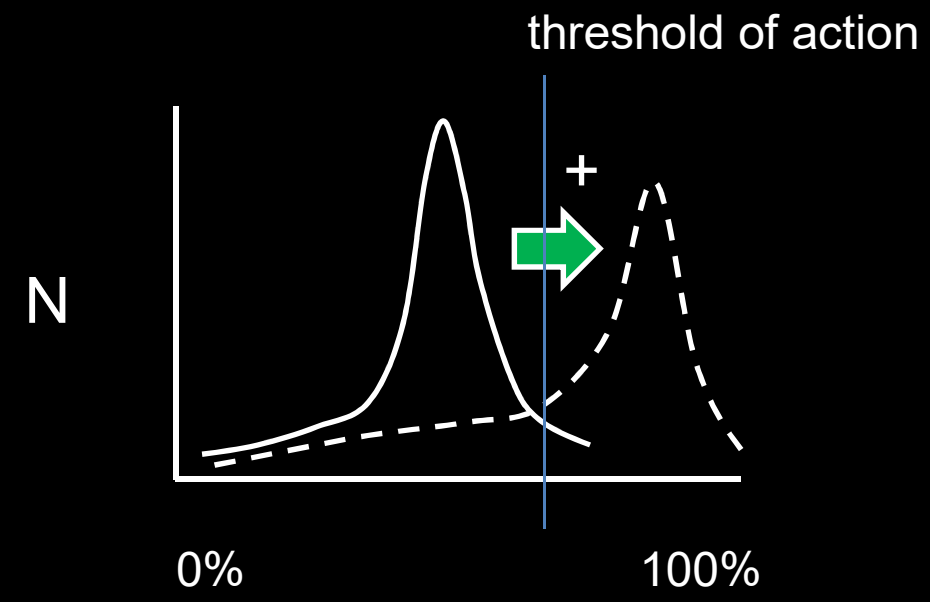
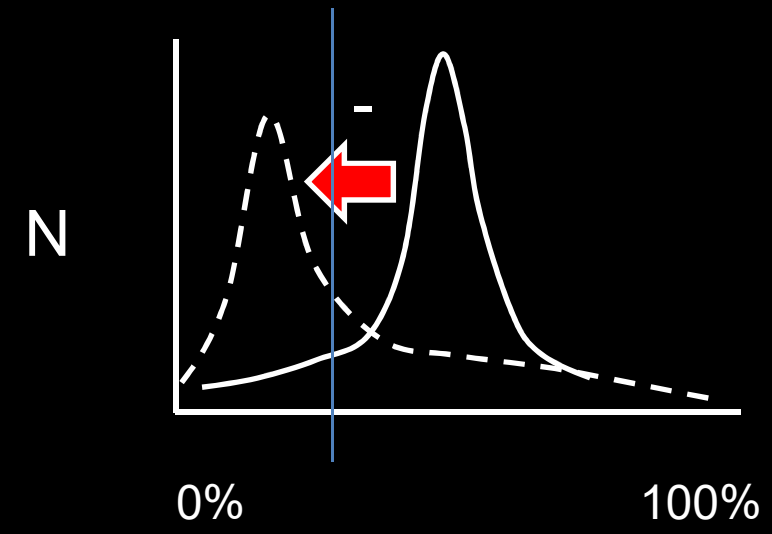
100%


threshold of action
+
N
0%
100%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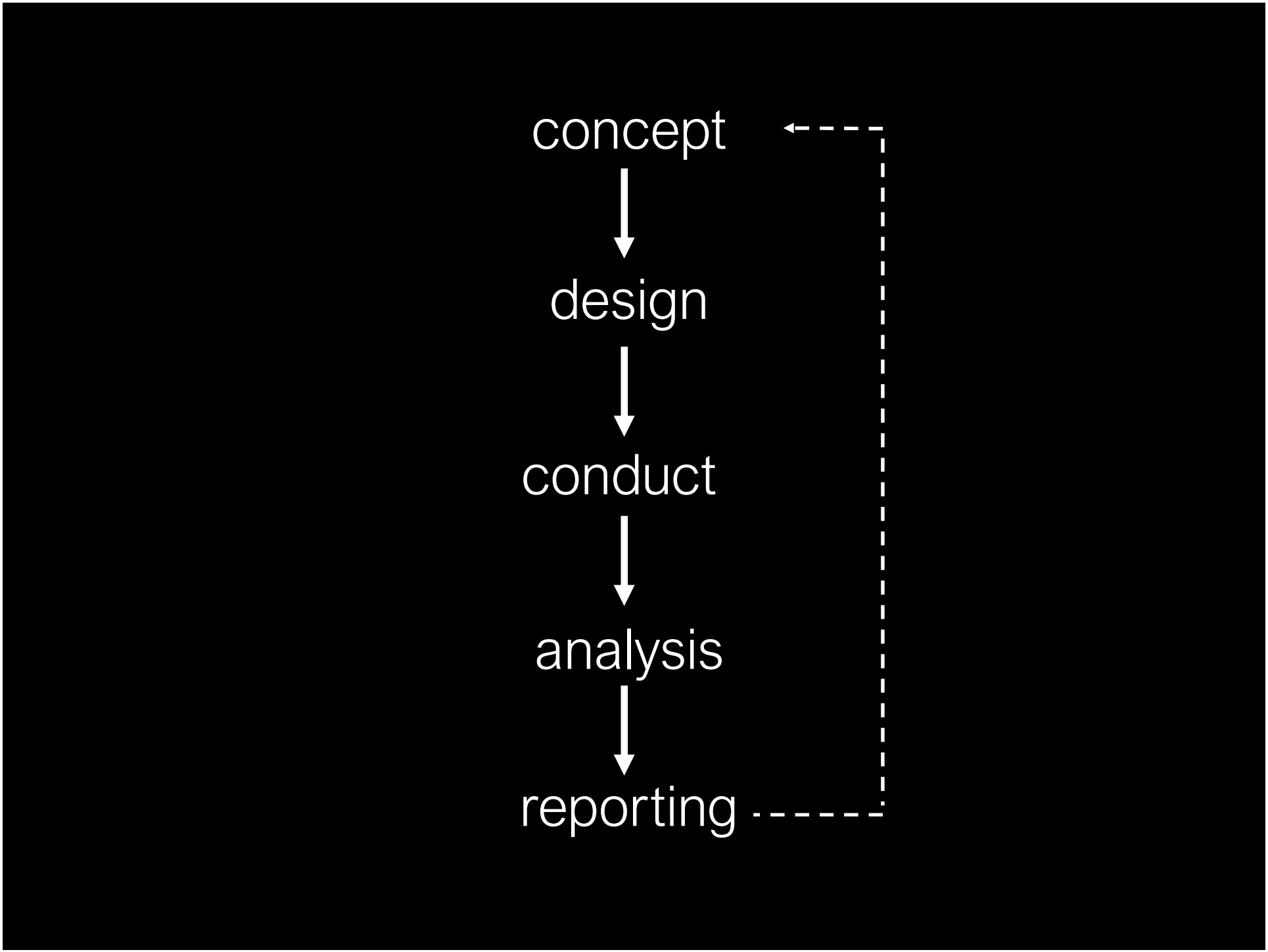
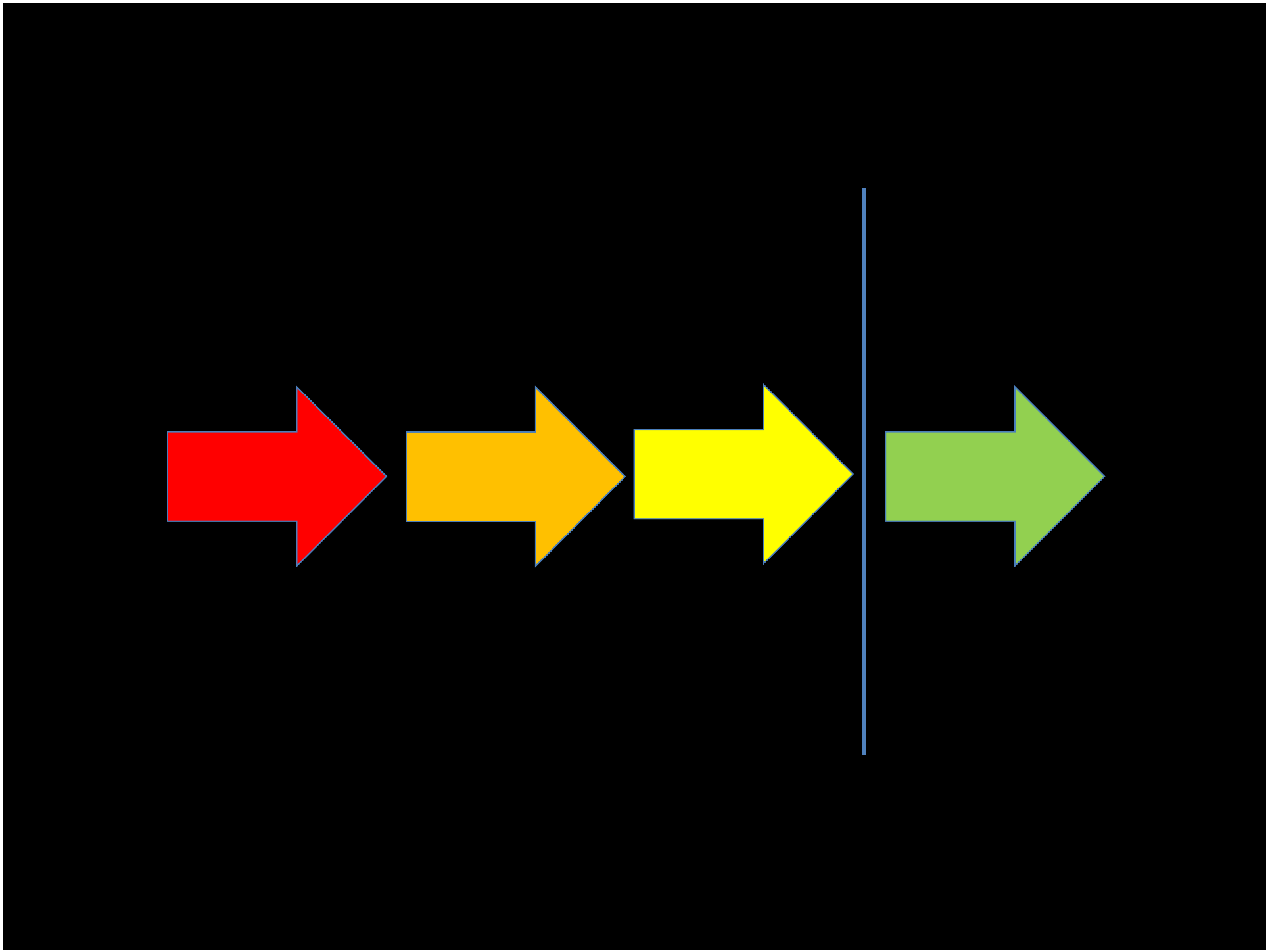
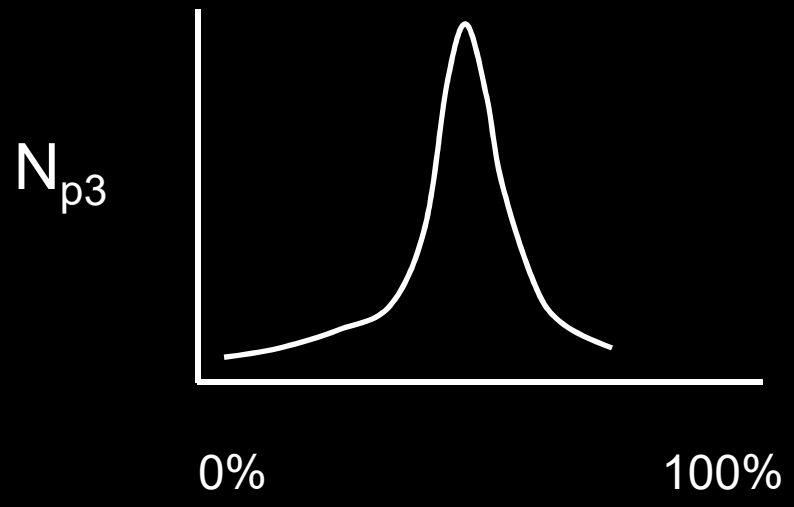

concept
design
conduct
analysis
reporting

4. theory of trajectories




N_{p3}
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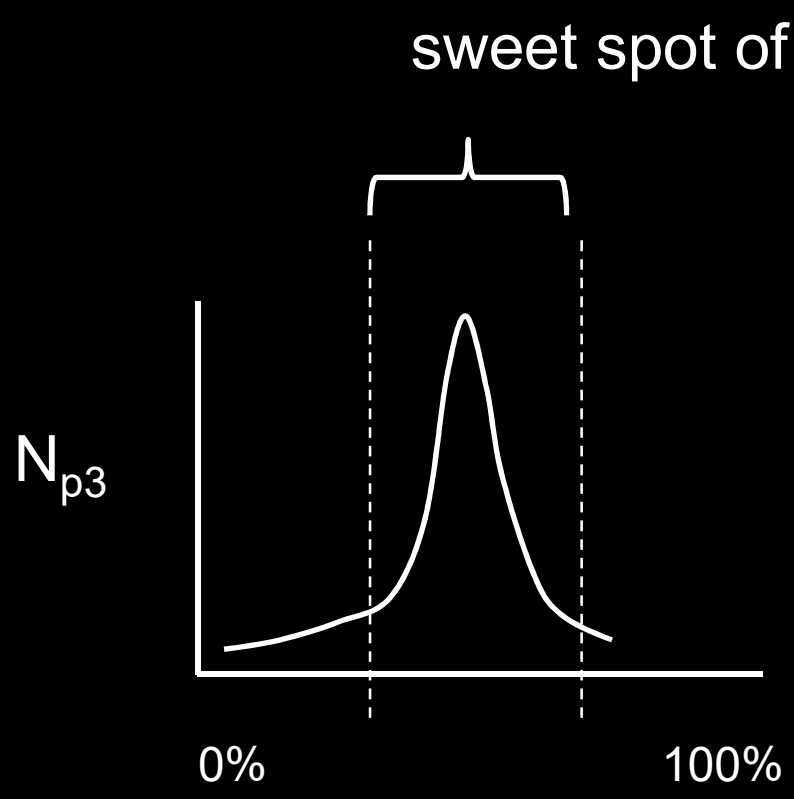
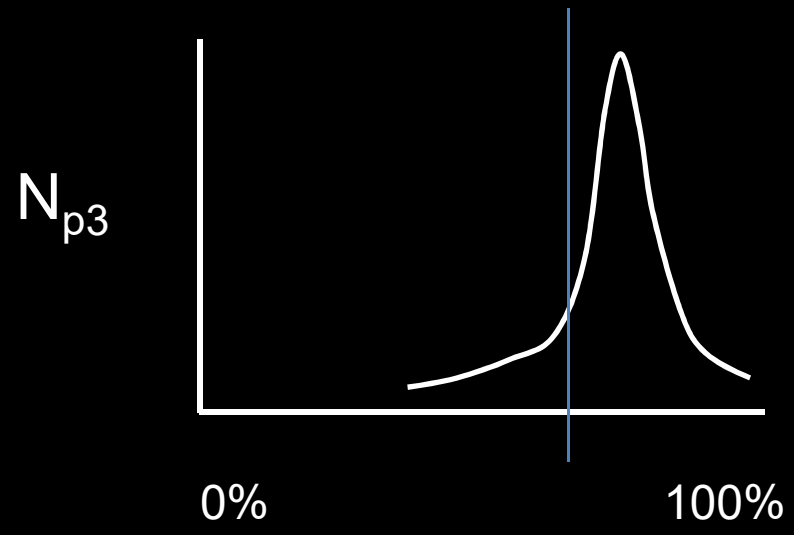
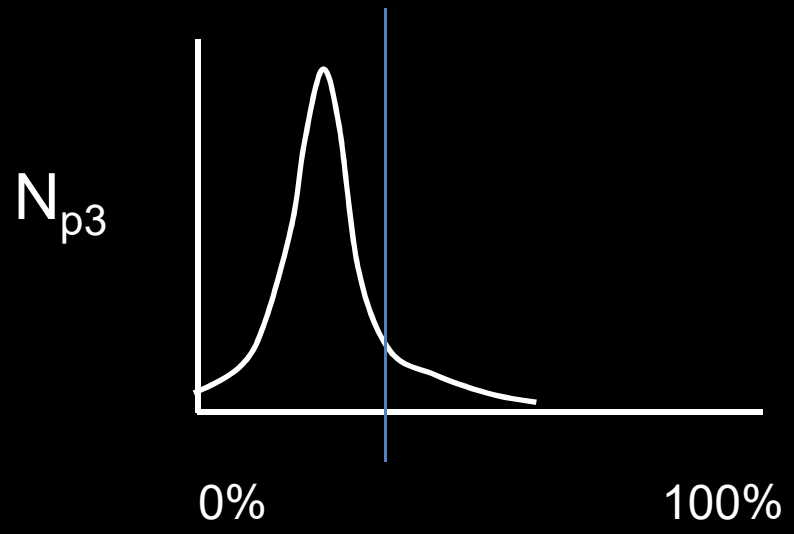
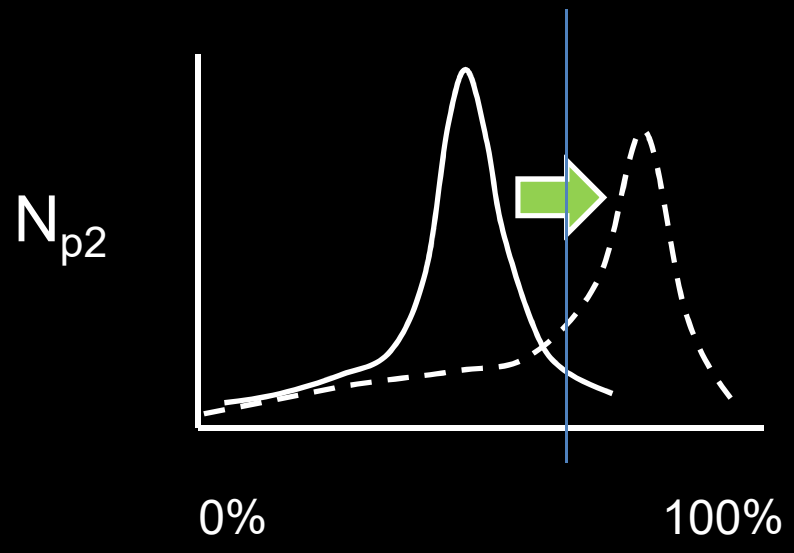
100%


sweet spot of uncertainty
N_{p3}
0%
100%


N_{p3}
0%
100%

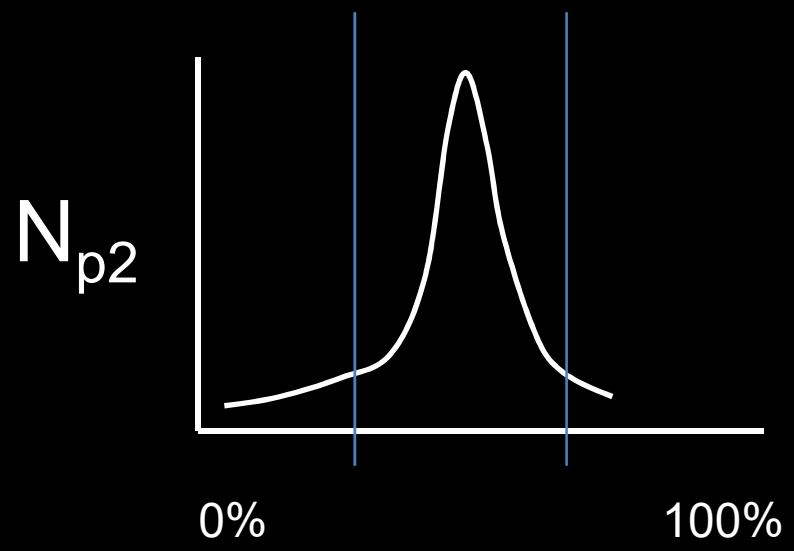

N_{p3}
0%
100%

- substitute for SoC
- large number of patients
- long duration
- many scientific resources


N_{p2}
0%
100%

- no substitution of SoC
- small number of patients
- short duration
- few scientific resources


N_{p2}
N_{p3}


N_{p2}
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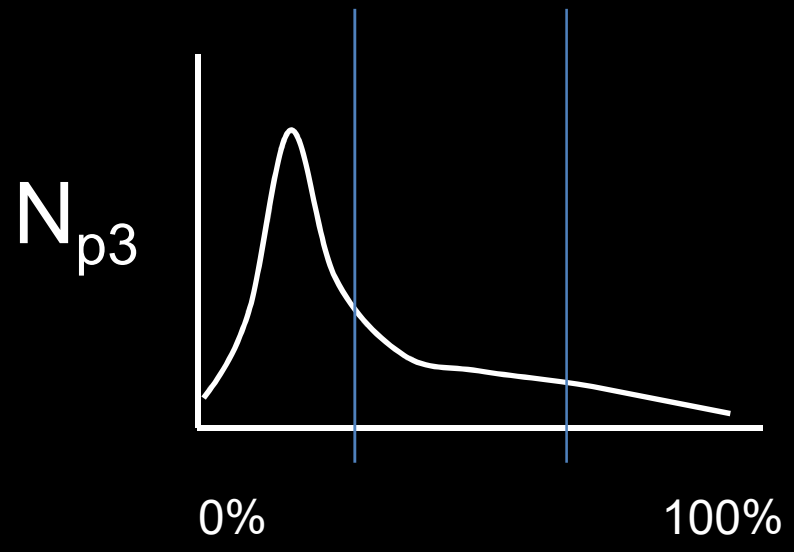
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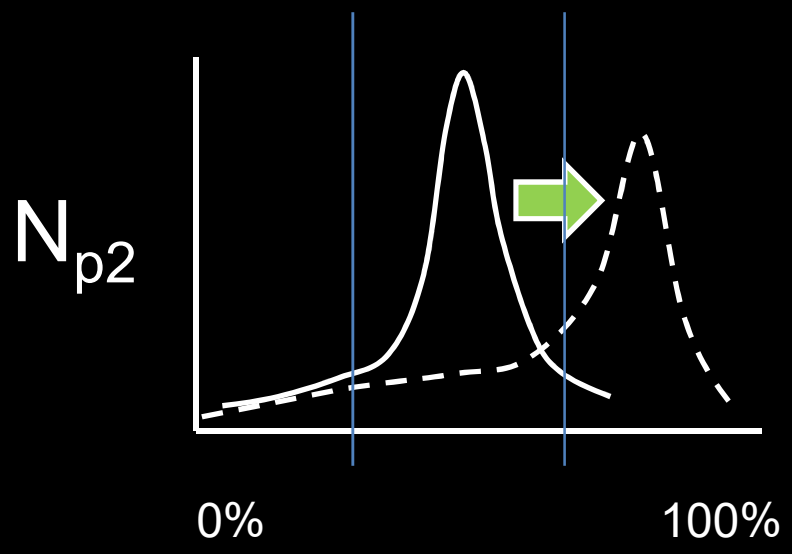
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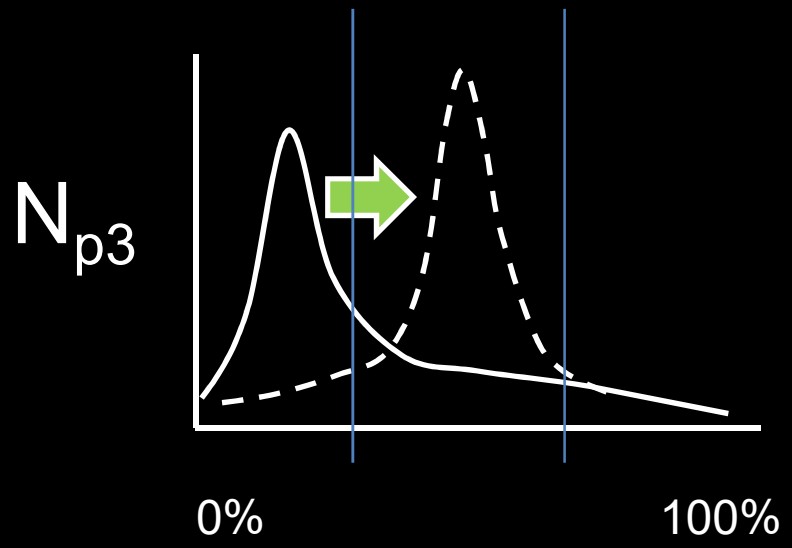
N_{p3}
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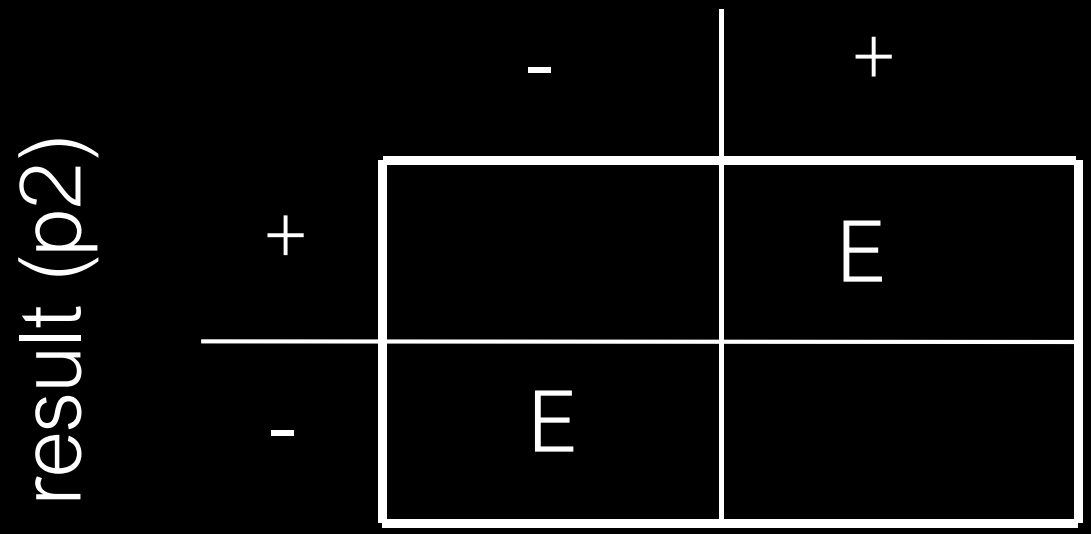
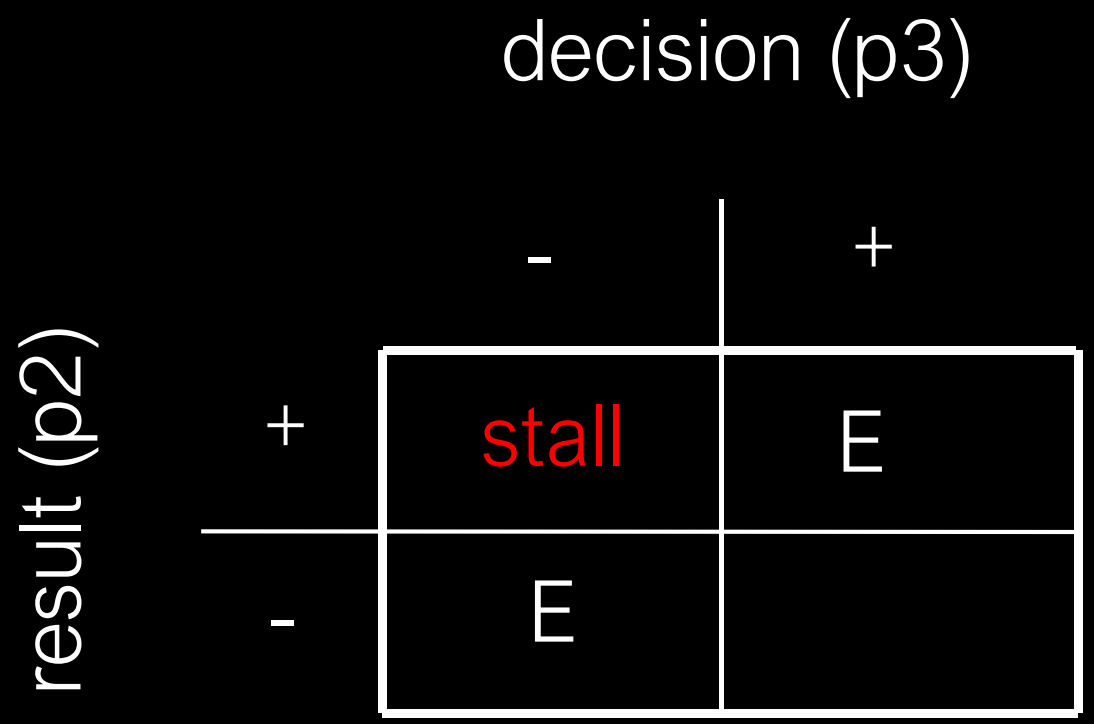
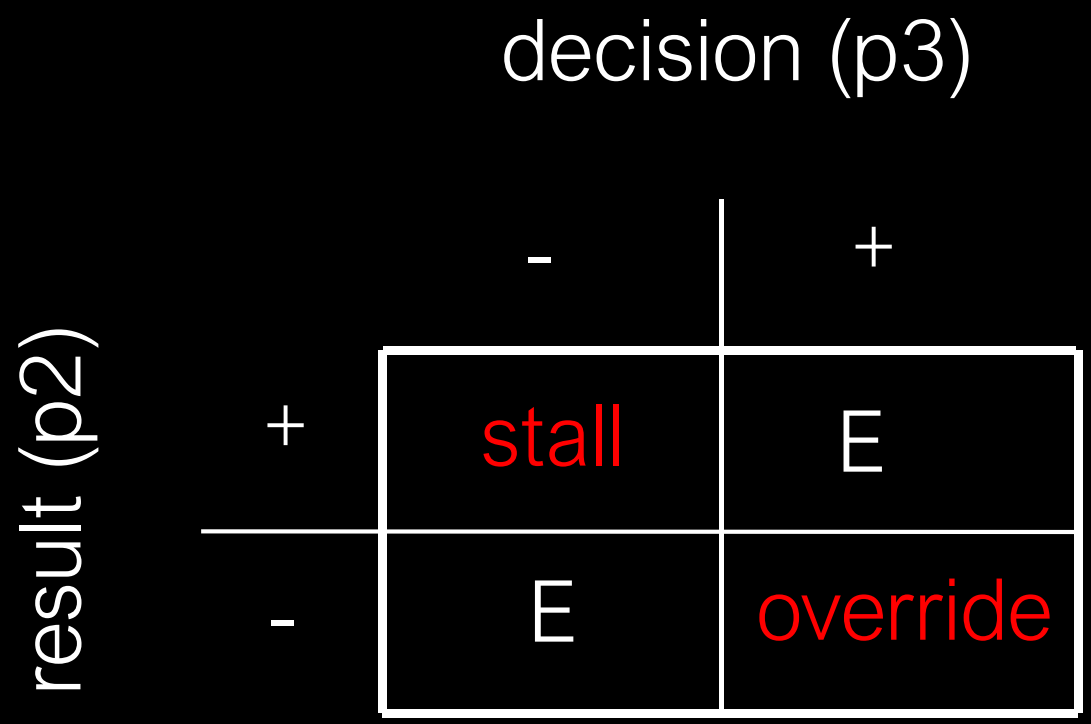
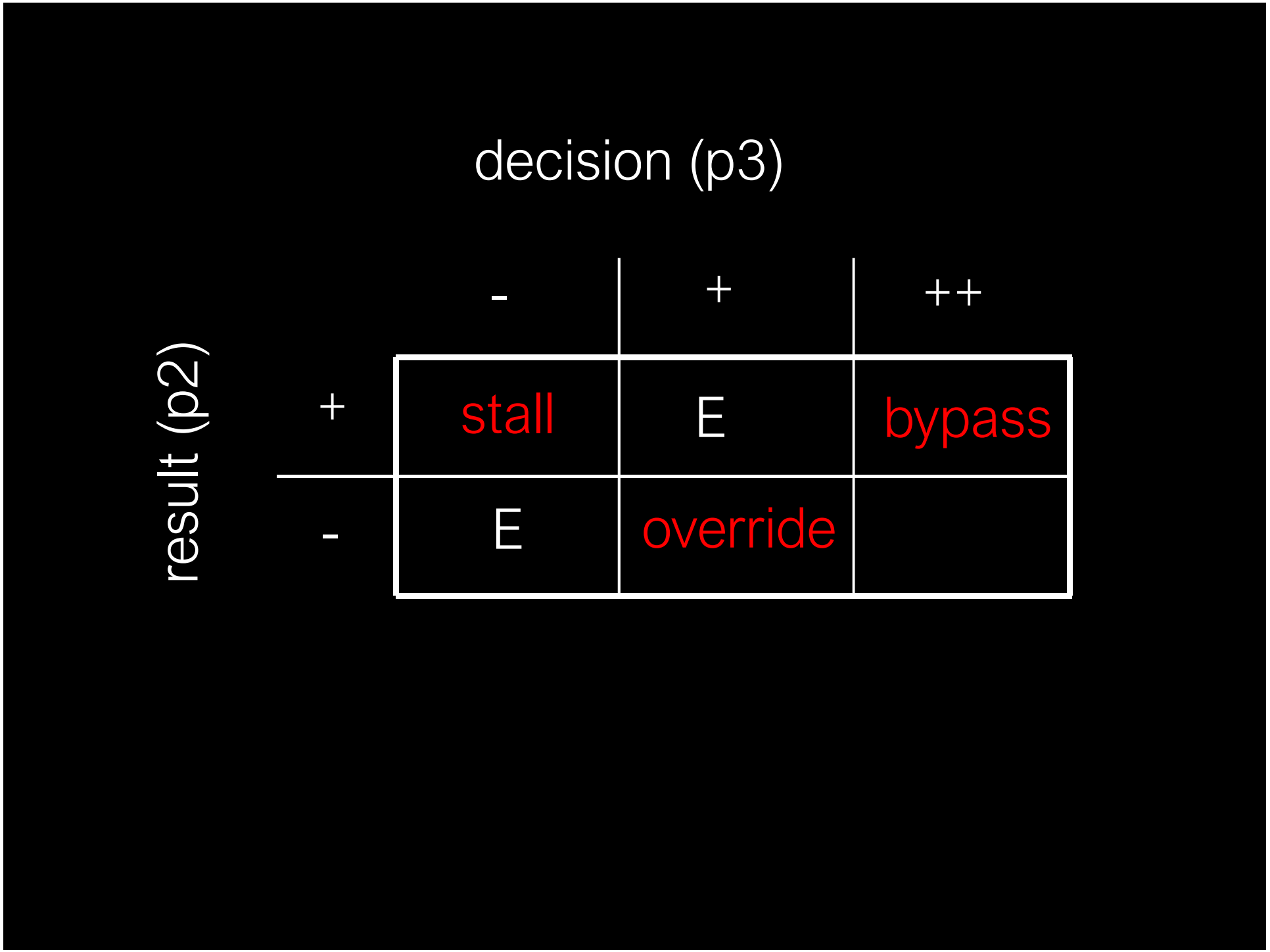
100%

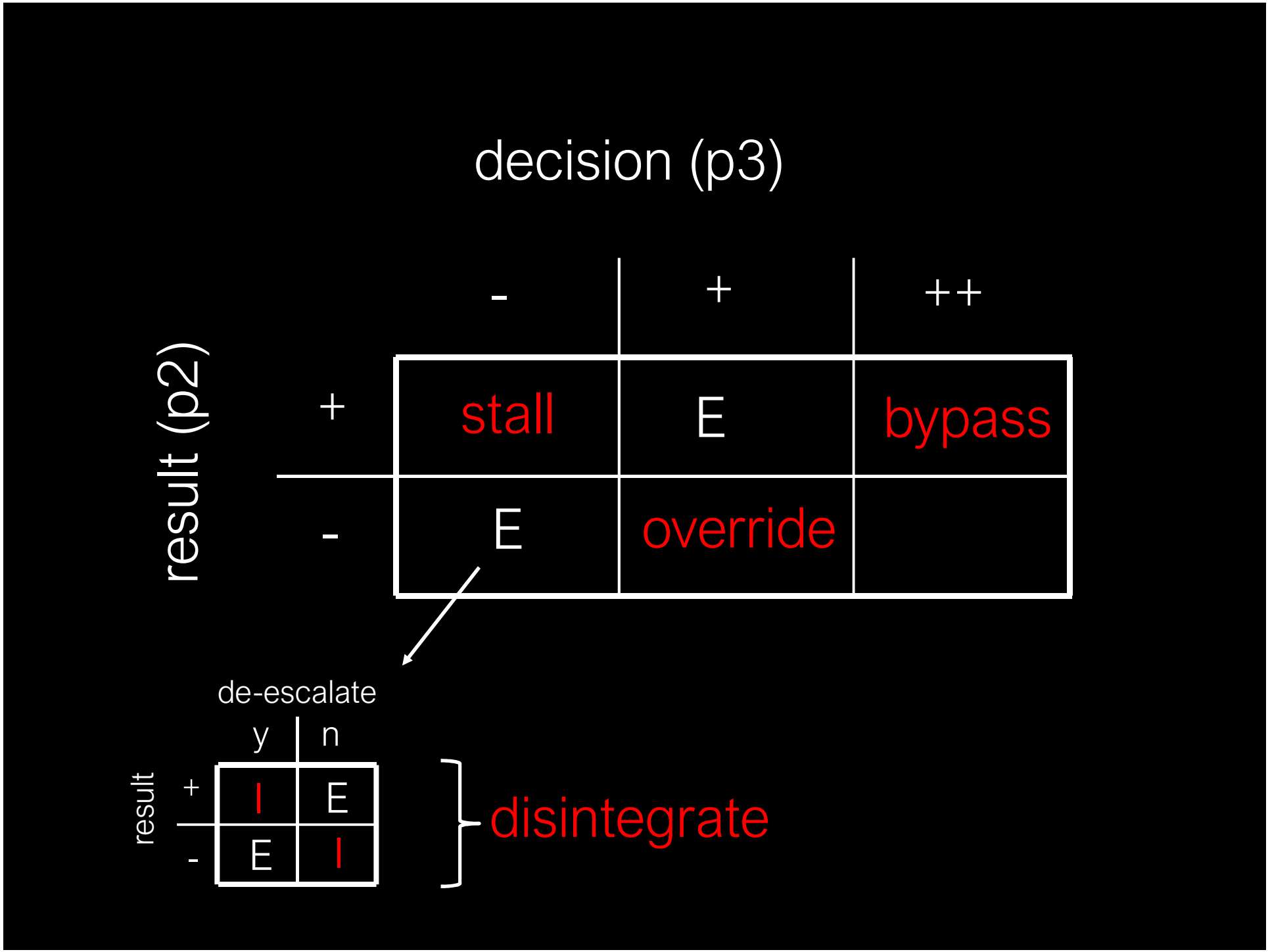
typology of inefficiencies


decision (p3)
-
+
result (p2)
+
E
-
E


decision (p3)
-
+
result (p2)
+
stall
E
-
E


decision (p3)
-
+
result (p2)
+
stall
E
-
E
override


decision (p3)
-
+
++
result (p2)
+
stall
E
bypass
-
E
override

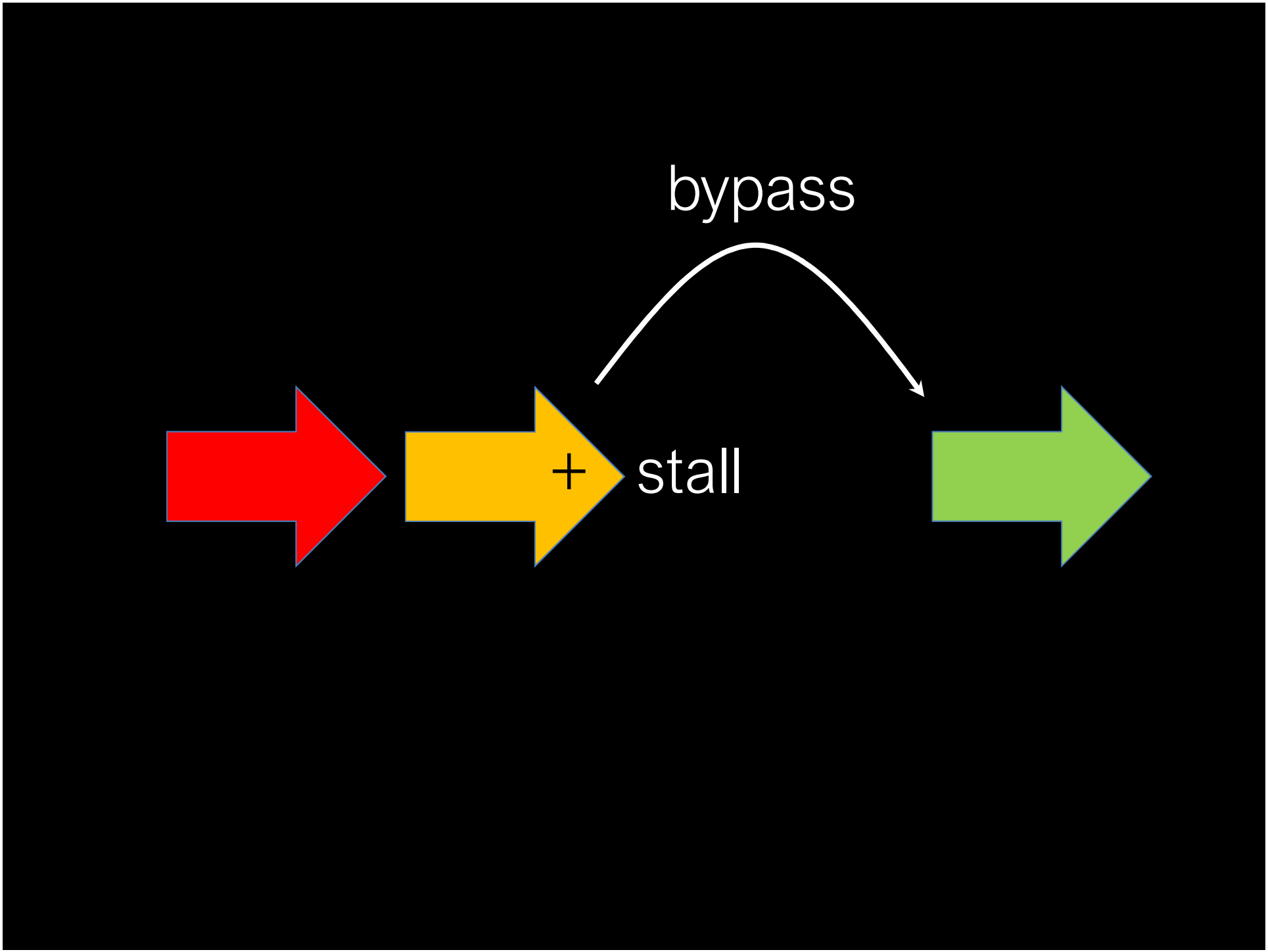

decision (p3)
-
+
++
result (p2)
+
stall
E
bypass
-
E
override
de-escalate
y
n
result
+
I
E
-
E
I
disintegrate

1) pts / animals in module

2) pts in modules after

5. prevalence of trajectory inefficiency

a) stall and bypass


bypass
+
stall

drug approval

Original Investigation | Oncology

Assessment of Outcomes Associated With the Use of Newly Approved Oncology Drugs in Medicare Beneficiaries

Angela K. Green, MD, MSc; Michael Curry, MS; Niti Trivedi, MPH; Peter B. Bach, MD, MAPP; Sham Mailankody, MBBS

[64.3%] White) and 9178 SEER-Medicare patients (mean age, 72.7 years; 4800 [52.3%] male; and 7437 [81.0% White]) were compared. Twenty-nine indications for 22 cancer drugs were included. Median overall survival among Medicare patients was shorter than among patients in the clinical trial intervention arm for 28 of 29 indications (median difference, −6.3 months; range, −28.7 to 2.7 months). Median duration of therapy among Medicare patients was shorter for 23 of the 27 indications with data available (median difference, −1.9 months; range, −12.4 to 1.4 months). For 9

drug approval

accelerated approval

Original Investigation FREE

August 15, 2017

Characteristics of Preapproval and Postapproval Studies for Drugs Granted Accelerated Approval by the US Food and Drug Administration

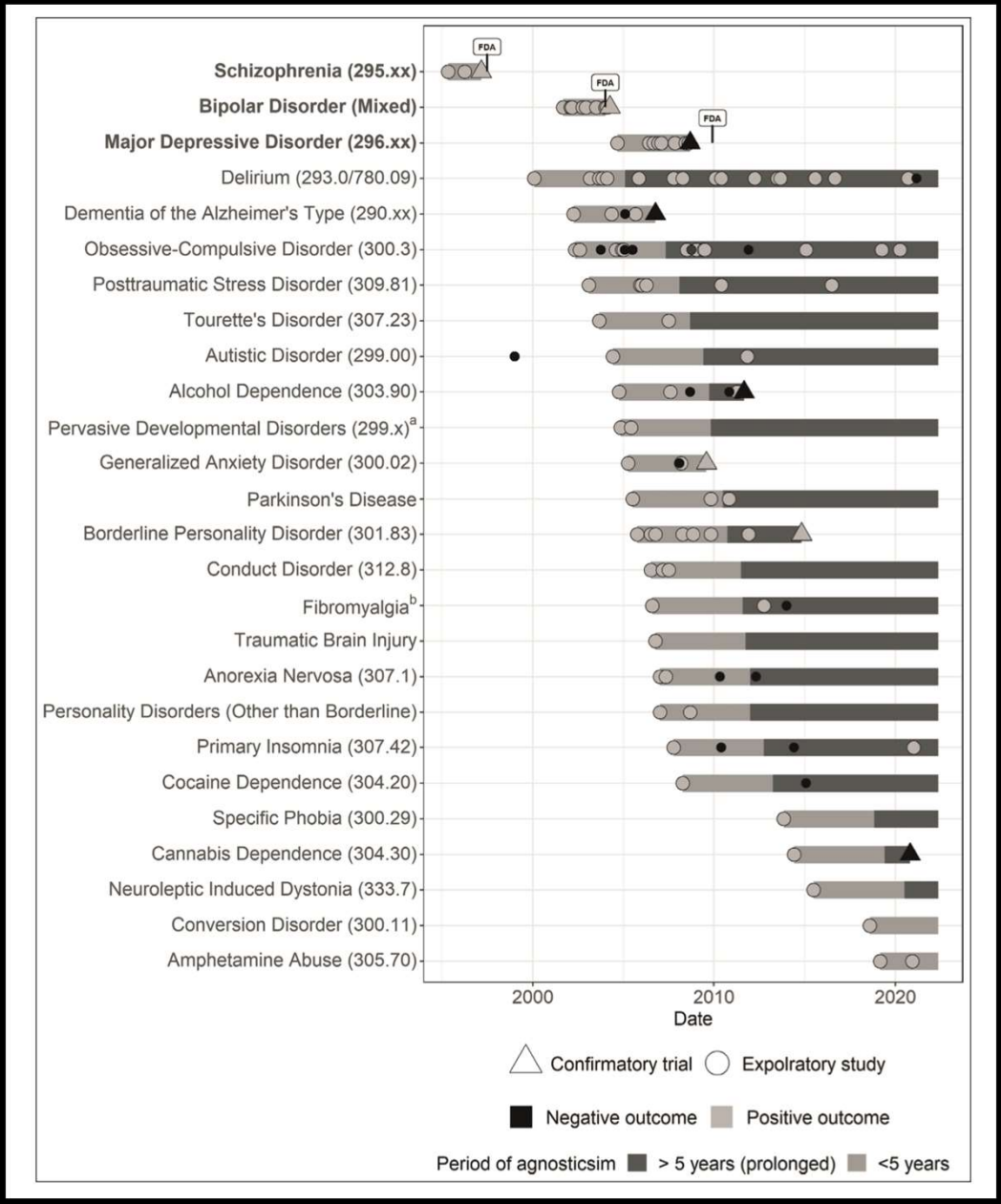
Huseyin Naci, PhD, MHS[1]; Katelyn R. Smalley, BSc[1]; Aaron S. Kesselheim, MD, JD, MPH[2]

JAMA 2017

50% confirmed
44% not randomized

many use surrogates

drug approval
accelerated approval
off label prescription



79% stall
29% bypass

drug approval
accelerated approval
off label prescription

late phase

REVIEW ARTICLE

Bypassing phase 2 in cancer drug development erodes the risk/benefit balance in phase 3 trials

Hannah Moyer[a], Merlin Bittlinger[a], Angela Nelson[a], Luciano Fernandez[a], Jacky Sheng[a], Yuetong Wang[a], Joseph C. Del Paggio[b], Jonathan Kimmelman[a,*]

JCE 2023
also Neurol 2024

25% p2 bypass
(31% in neuro)

drug approval
accelerated approval
off label prescription

late phase

early phase

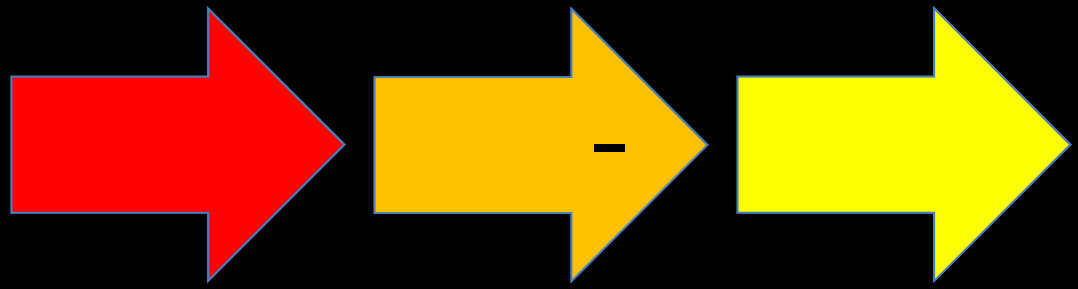
How well are Phase 2 cancer trial publications supported by preclinical efficacy evidence?

Michael Pratte, Sylviya Ganeshamoorthy, Benjamin Carlisle and Jonathan Kimmelman

Int J Cancer 2019

69% p2 trials: no preclinical support
51%: no preclinical or phase 1

b) override



drug approval

Original Investigation

Association of Advisory Committee Votes With US Food and Drug Administration Decision-Making on Prescription Drugs, 2010-2021

C. Joseph Ross Daval, JD; Theodore W. Teng; Massimiliano Russo, PhD; Aaron S. Kesselheim, MD, JD, MPH

JAMA HealthForum 2023
also J Gen Int Med 2023

33% FDA o/rides expert recs
40% EMA o/rides expert recs

drug approval
accelerated

Regulatory and clinical consequences of negative confirmatory trials of accelerated approval cancer drugs: retrospective observational study

Bishal Gyawali,[1,2] Benjamin N Rome,[2] Aaron S Kesselheim[2]

BMJ 2018

33% of time, FDA does not change label after (-) confirmatory trials

drug approval
accelerated approval

late phase

REVIEW ARTICLE

Bypassing phase 2 in cancer drug development erodes the risk/benefit balance in phase 3 trials

Hannah Moyer[a], Merlin Bittlinger[a], Angela Nelson[a], Luciano Fernandez[a], Jacky Sheng[a], Yuetong Wang[a], Joseph C. Del Paggio[b], Jonathan Kimmelman[a,*]

JCE 2023; also Neurology 2024

25% P2 override (cancer)
15% P2 override (neurology)

drug approval
accelerated approval

late phase

early phase

Original Investigation | Oncology

Costs and Causes of Oncology Drug Attrition With the Example of Insulin-Like Growth Factor-1 Receptor Inhibitors

Valerie Jentzsch, MSc; Leeza Osipenko, PhD; Jack W. Scannell, DPhil; John A. Hickman, DSc

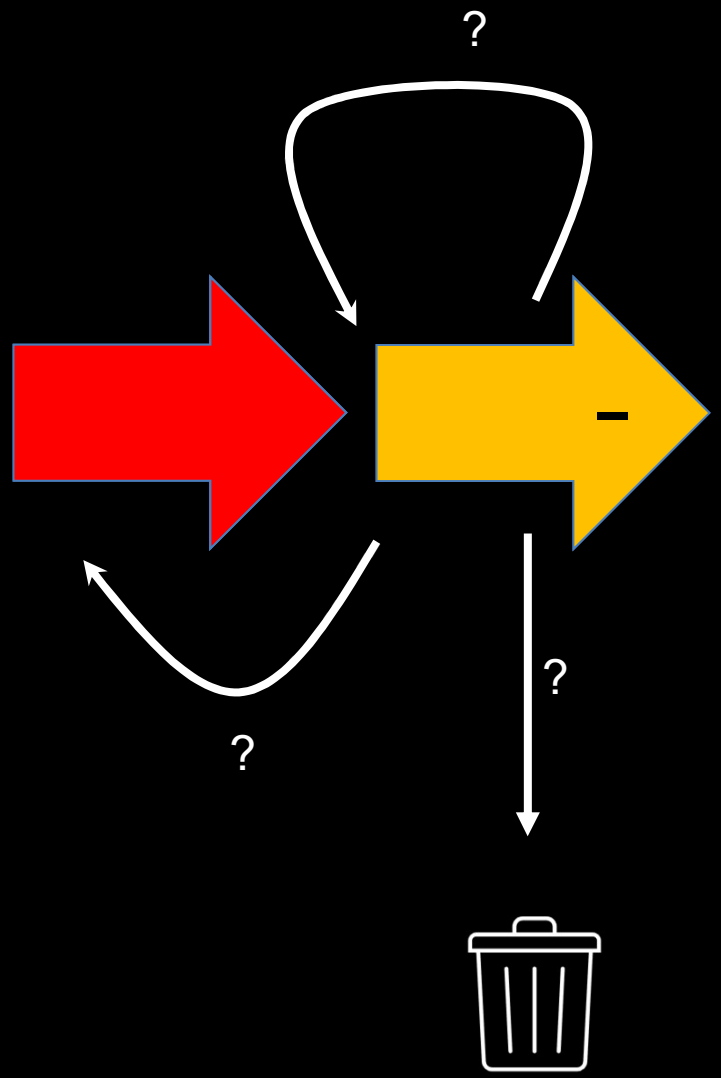
JAMA-Open 2023

Preclinical Efficacy Failure of Human CNS-Derived Stem Cells for Use in the Pathway Study of Cervical Spinal Cord Injury

Aileen J. Anderson,[1,2,3,4,*] Katja M. Piltti,[1,3] Mitra J. Hooshmand,[1,3] Rebecca A. Nishi,[1,3] and Brian J. Cummings[1,2,3,4]

Stem Cell Reports 2017

c) disintegration



Publication and Reporting Conduct for Pharmacodynamic Analyses of Tumor Tissue in Early-Phase Oncology Trials

Georgina A. Freeman[1] and Jonathan Kimmelman[2]

CCR 2012

19% PD not published
23% incompletely published

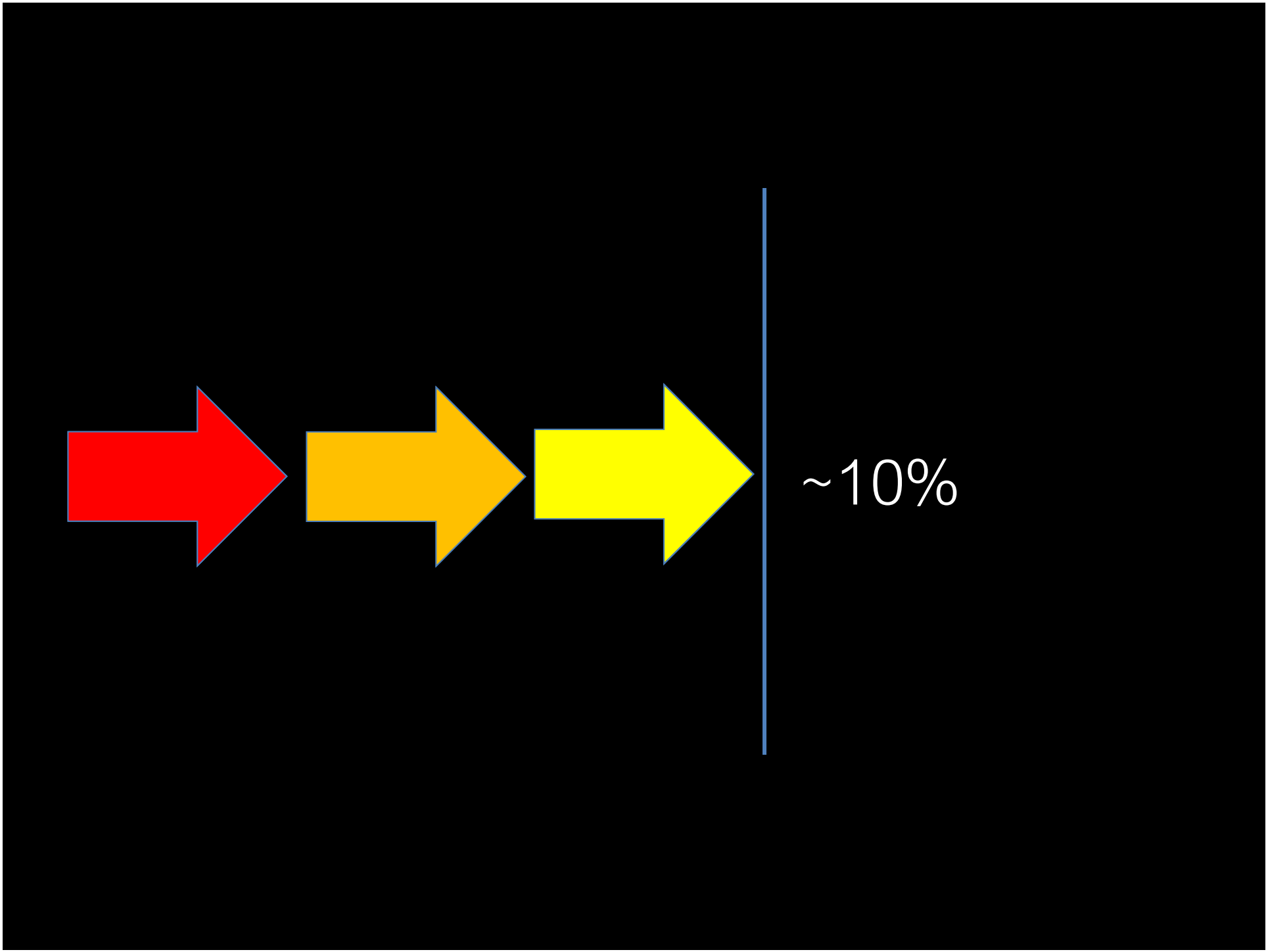
Impact of pharmacodynamic biomarkers in immuno-oncology phase 1 clinical trials

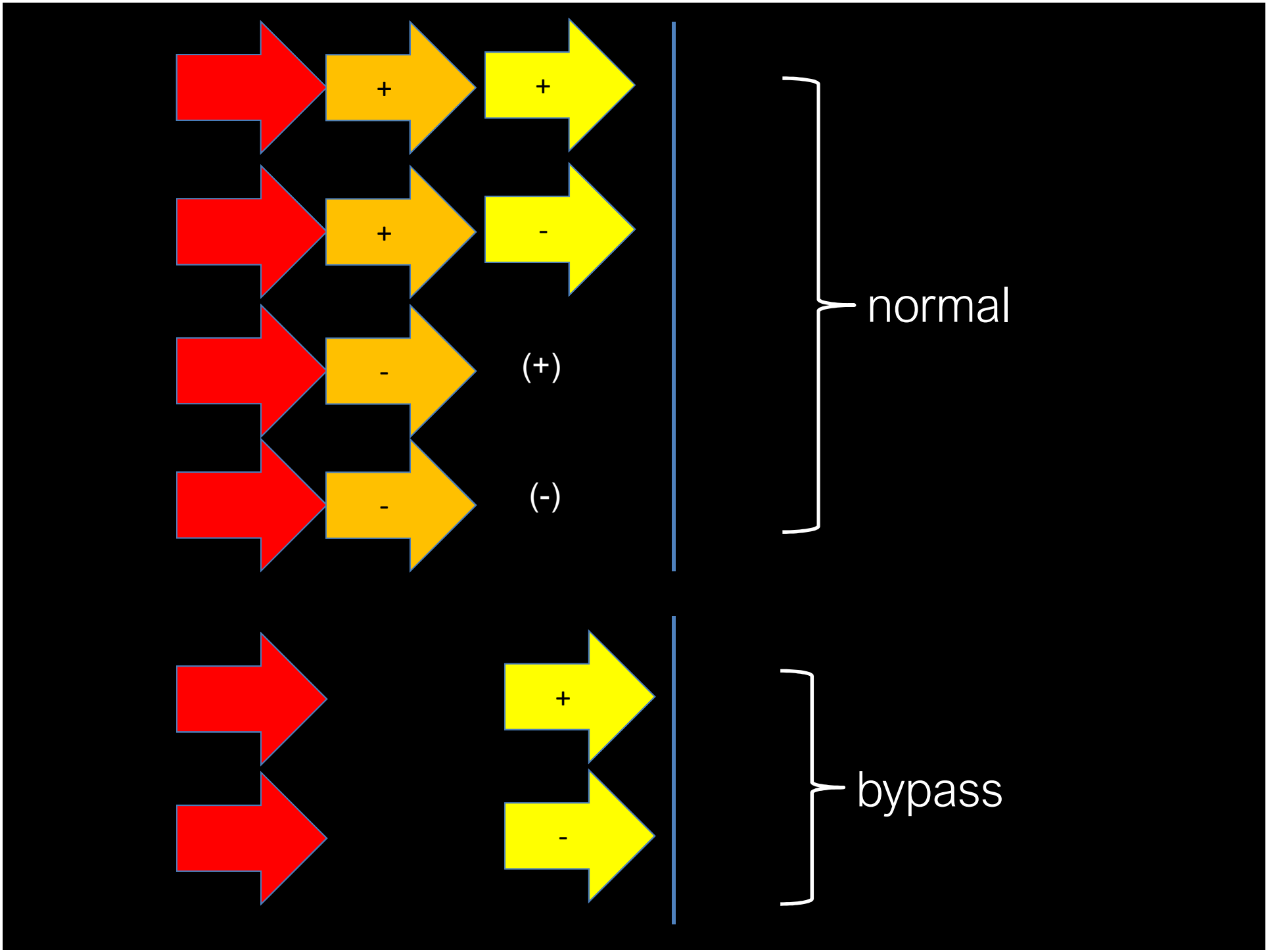
Abdulazeez Salawu [a,1], Alberto Hernando-Calvo [a,1], Rachel Y. Chen [b], Daniel V. Araujo [c], Marc Oliva [d], Zhihui A. Liu [a], Lillian L. Siu [a,*]

EJC 2022

8% referenced in subsequent pubs

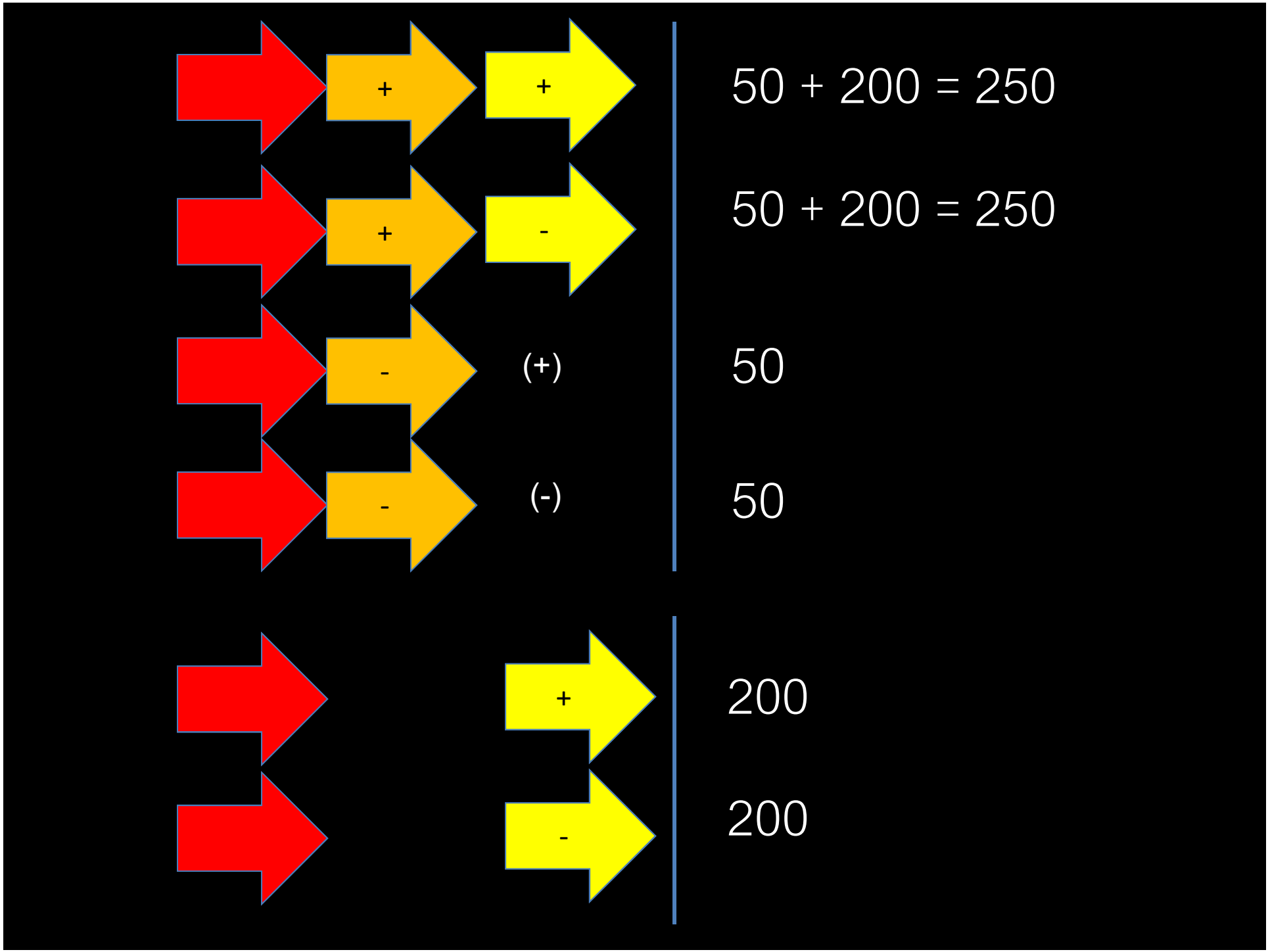
6. integrated view

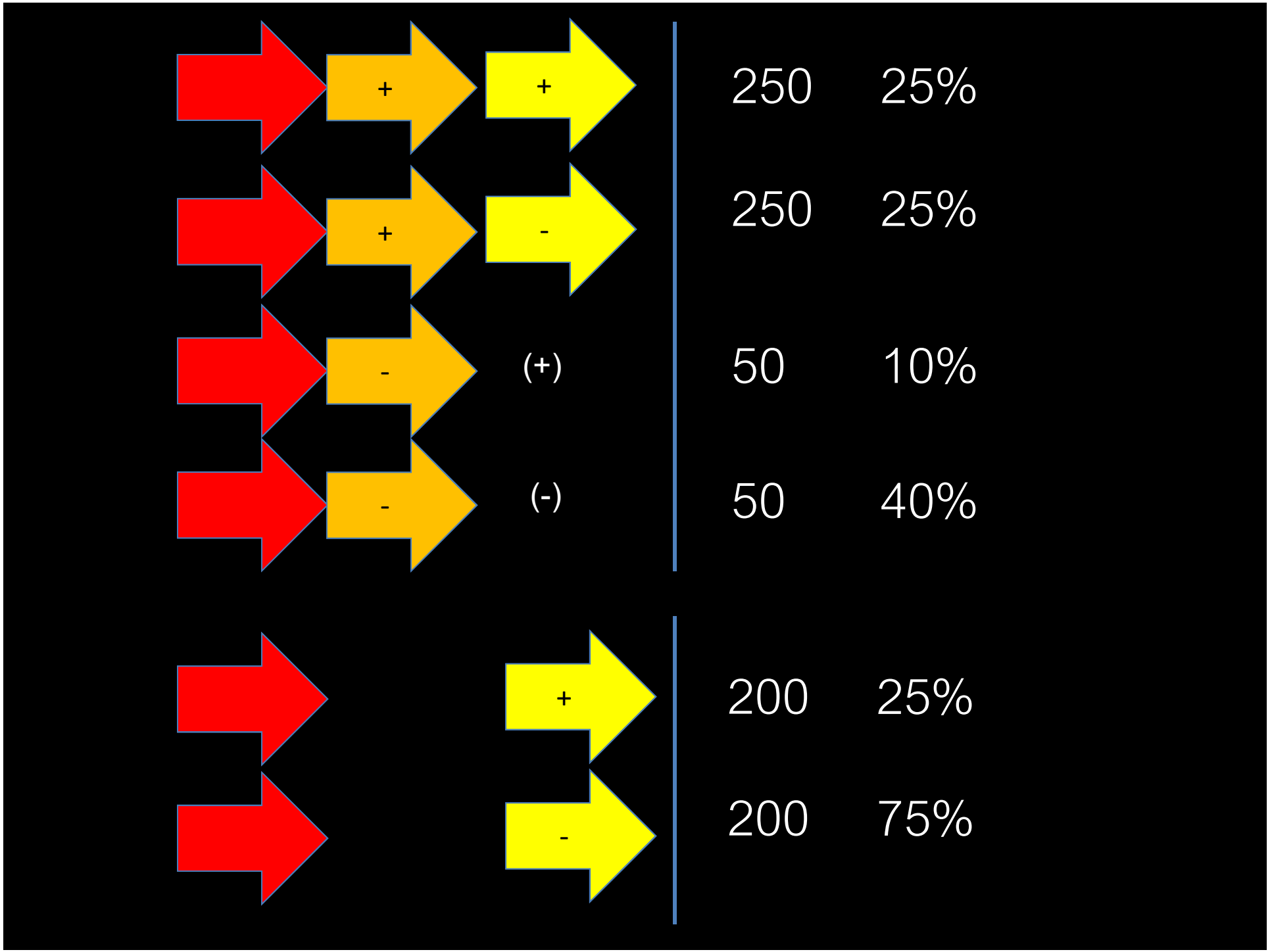

~10%


+
+
+
-
-
(+)
-
(-)
normal
+
-
bypass

assume:

- p2 trials are 25% the size of p3 trials
- all RCTs have 50% chance of (+), but…
- P2 results contain signal, e.g.
  - chance of (+) P3 falls to 20% if P2 is (-)
  - cost of false (-) in P2 is acceptable (i.e. 80% power)


+
+
50 + 200 = 250
+
-
50 + 200 = 250
-
(+)
50
-
(-)
50
+
200
-
200


+
+
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25%
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(+)
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10%
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(-)
50
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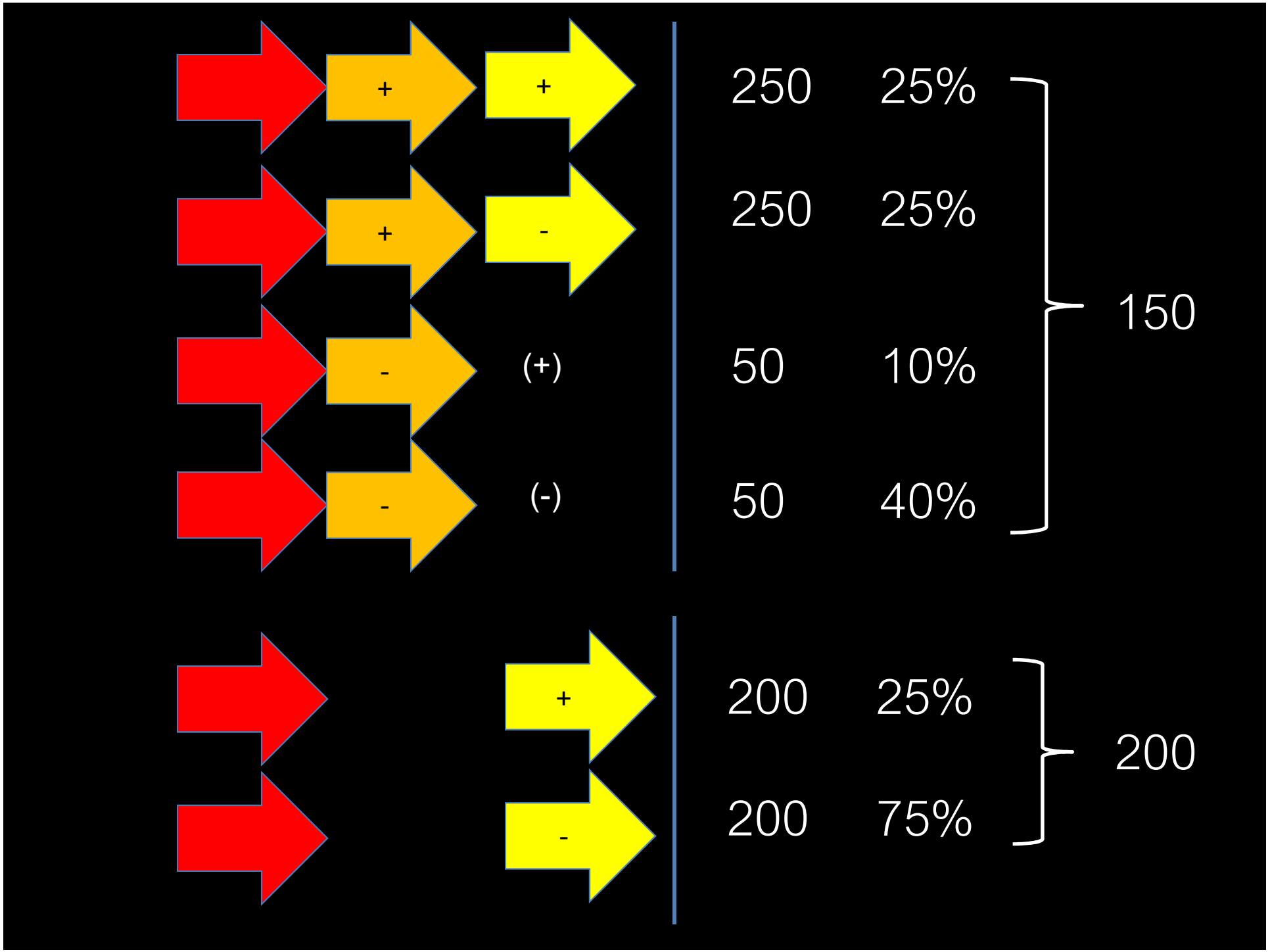
25%
-
200
75%


+
+
250
25%
+
-
250
25%
150
-
(+)
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(-)
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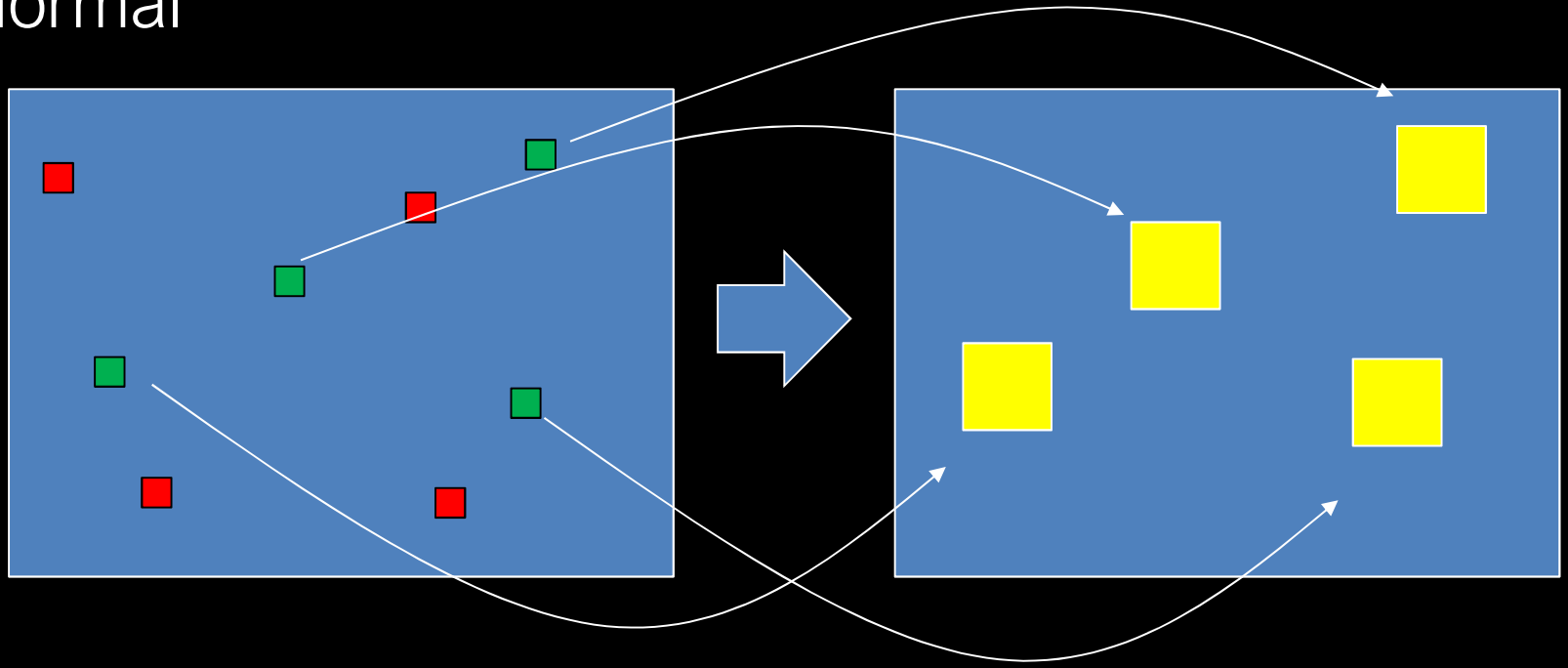
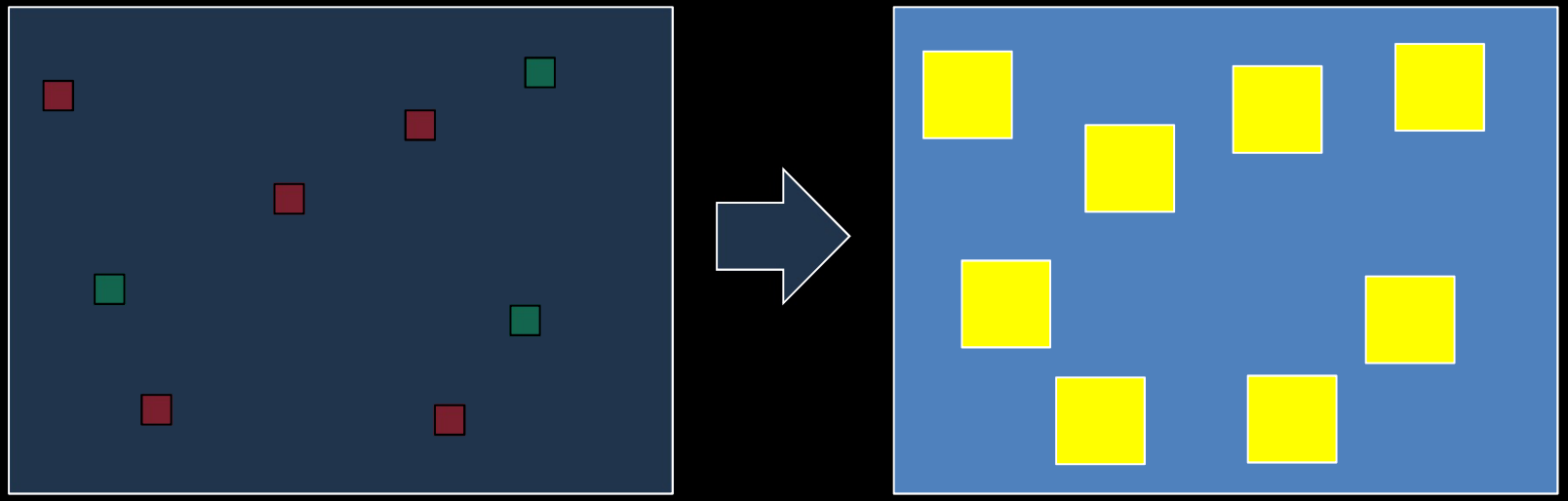
+
200
25%
200
-
200
75%

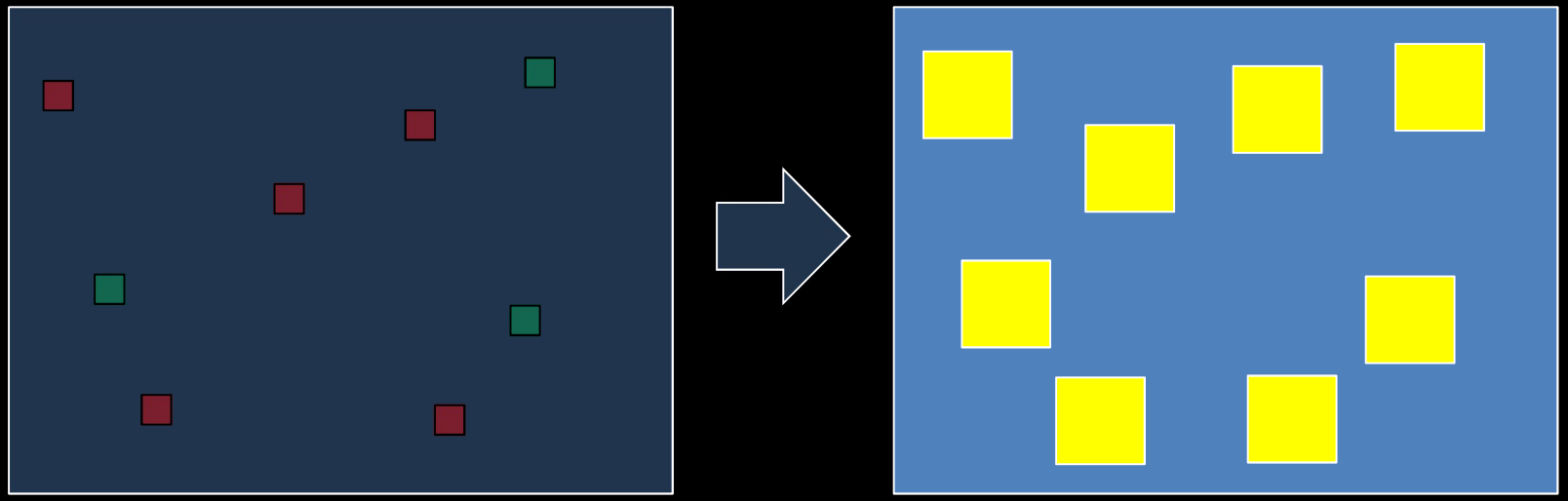
normal



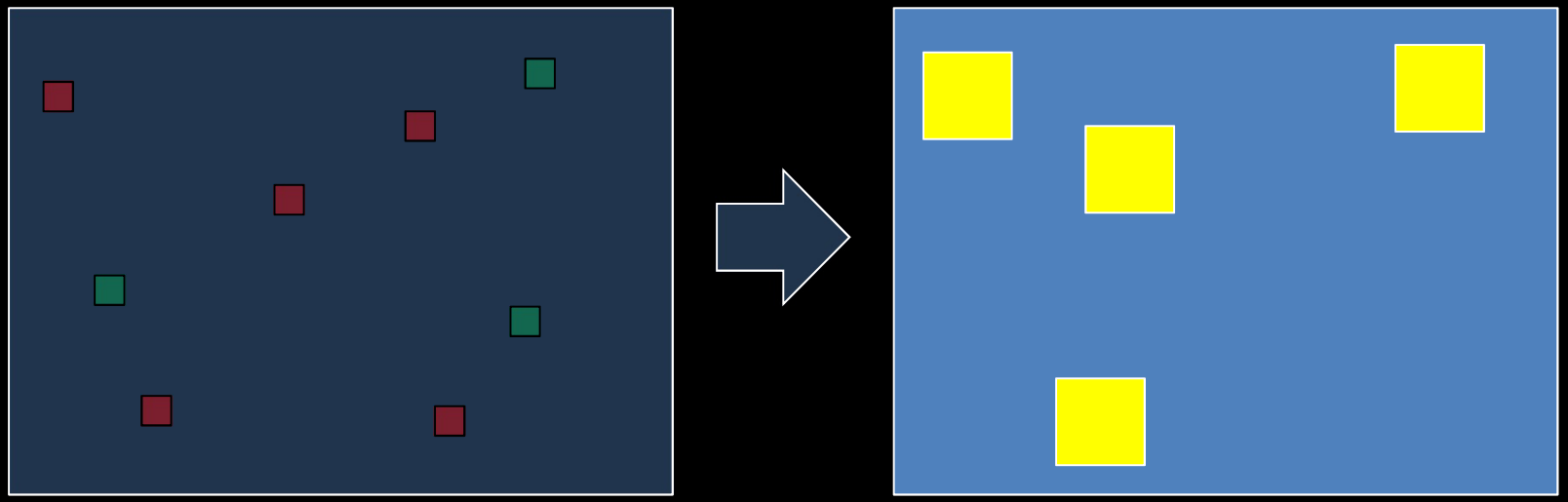
bypass (1)



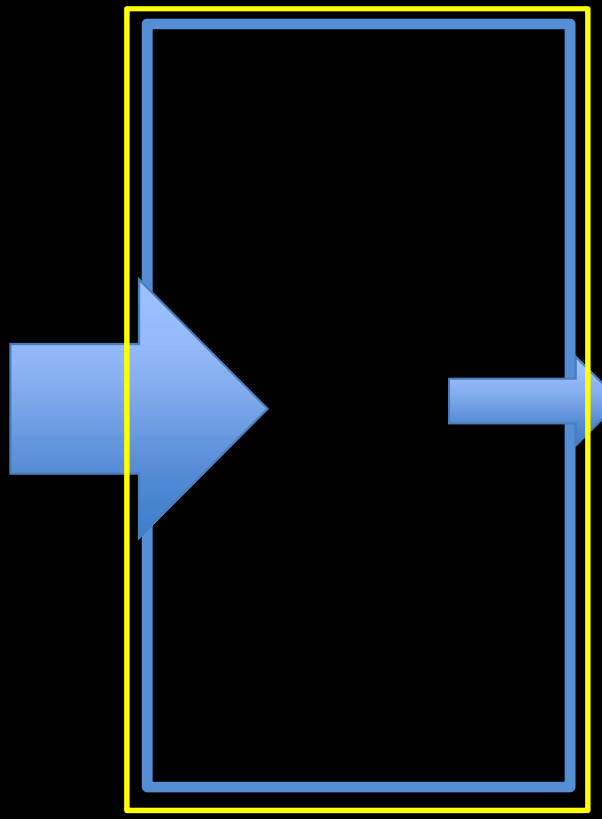
bypass (1)



bypass (2)



research



>welfare
>labour
>opportunity
<time (3.5 yrs)
…for bypass

conclusion
about
trajectory

7. tending the machine

economics

regulatory approval

regulatory approval
funding decisions
ethics approval

academic medical centres

cognitive

meta-research / visibility
economic analyses

meta-research / visibility
economic analyses

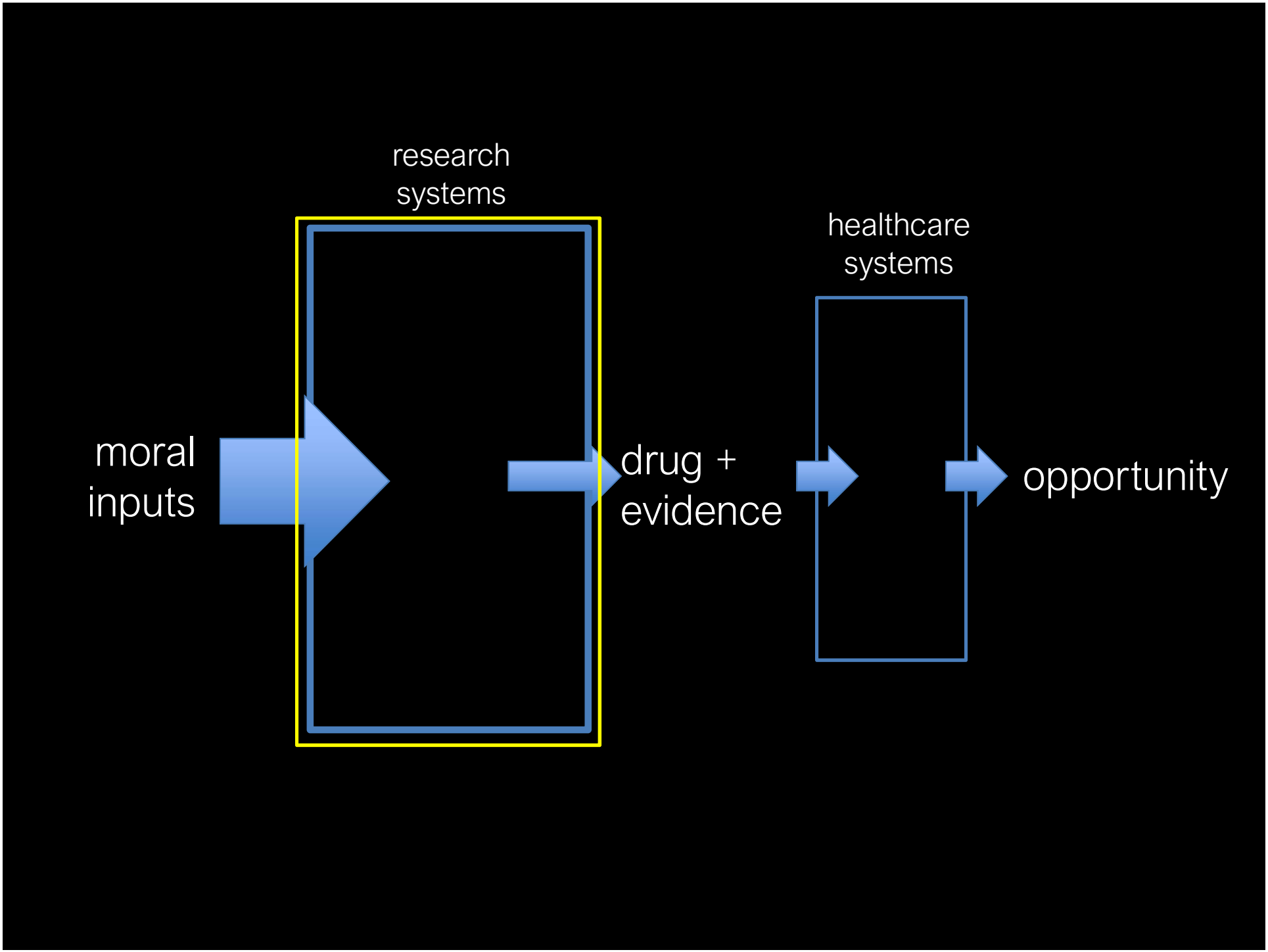
solicit info about trajectories
disclose it in consent

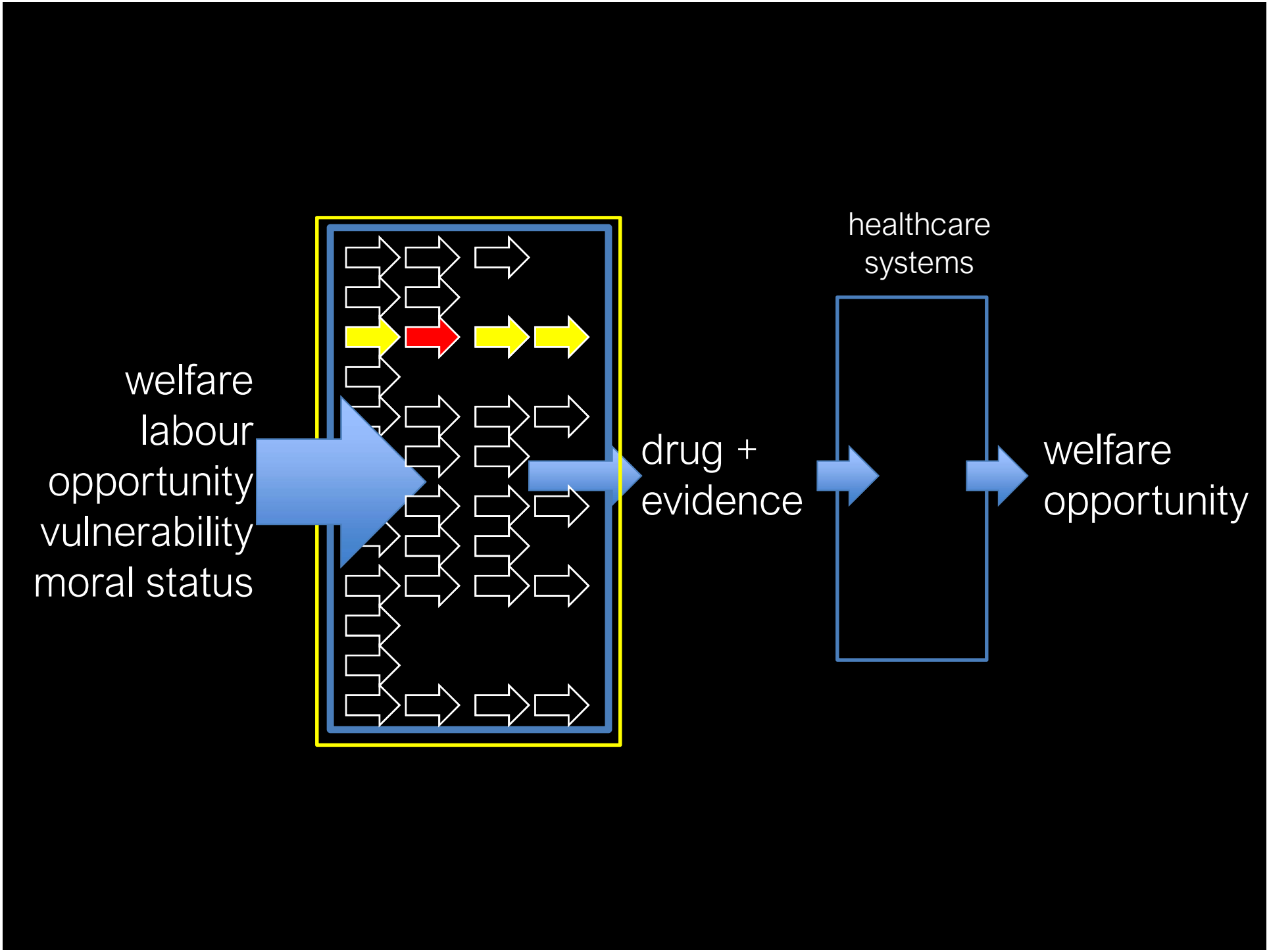
meta-research / visibility
economic analyses

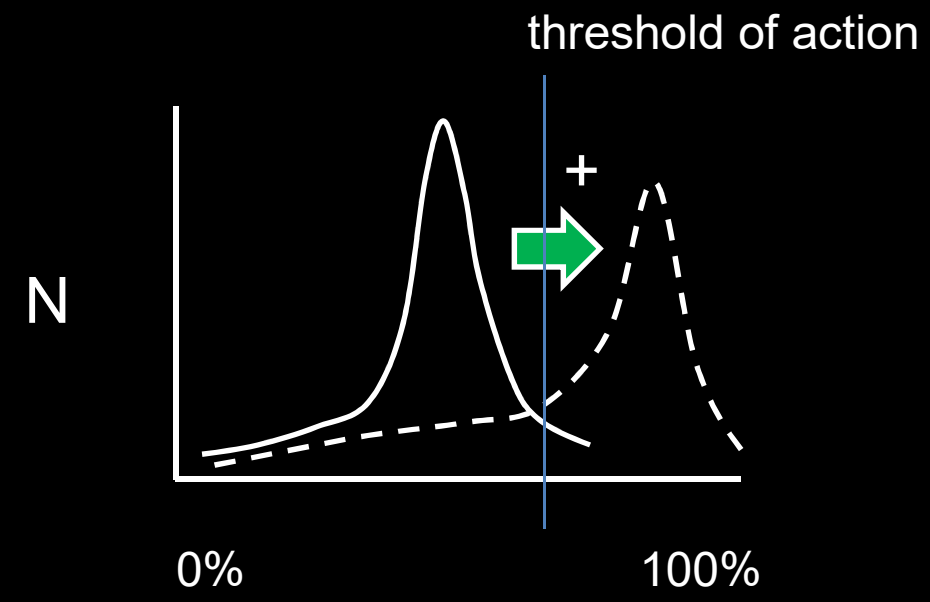
solicit info about trajectories
disclose it in consent

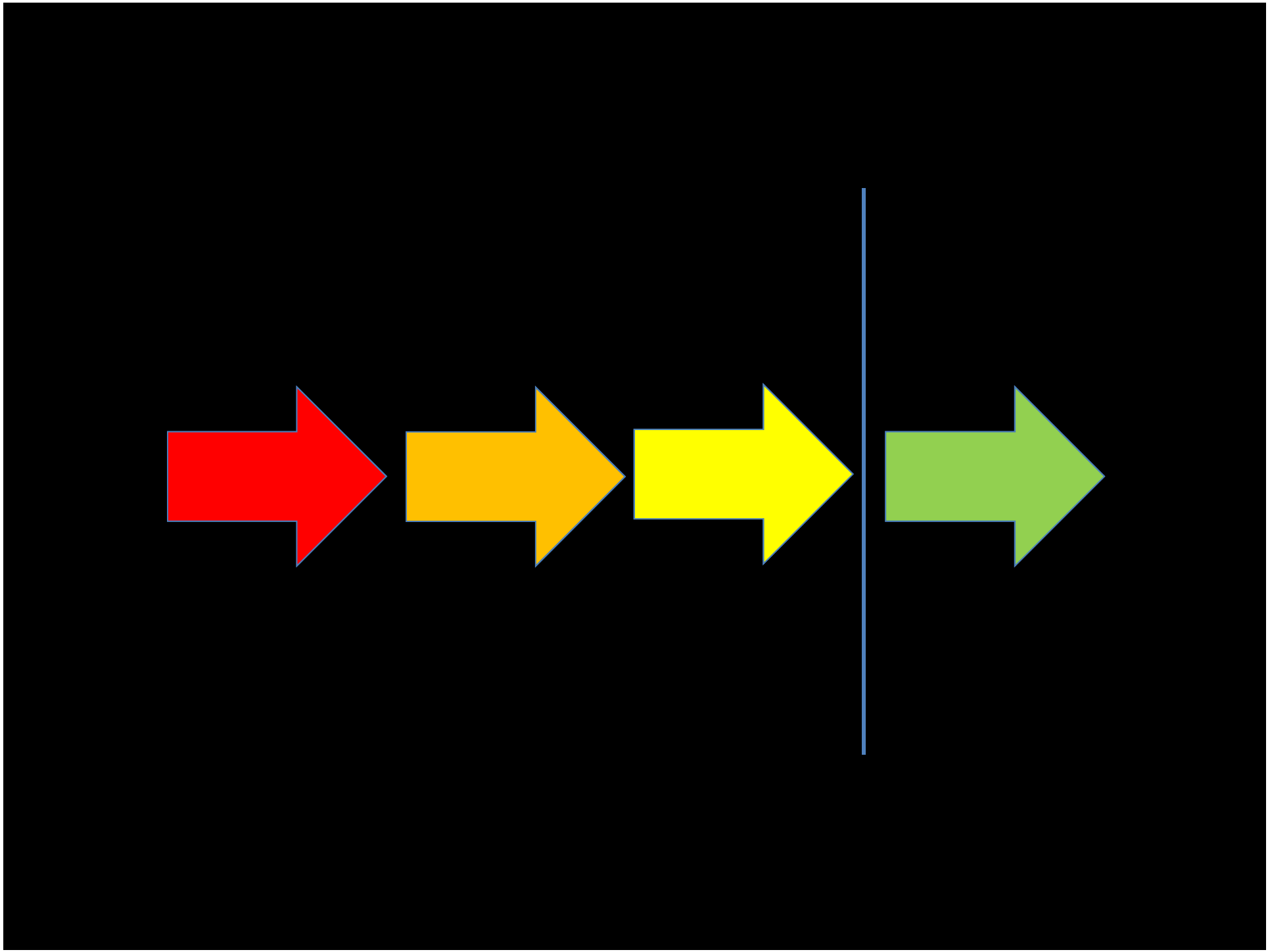
clear moral analysis

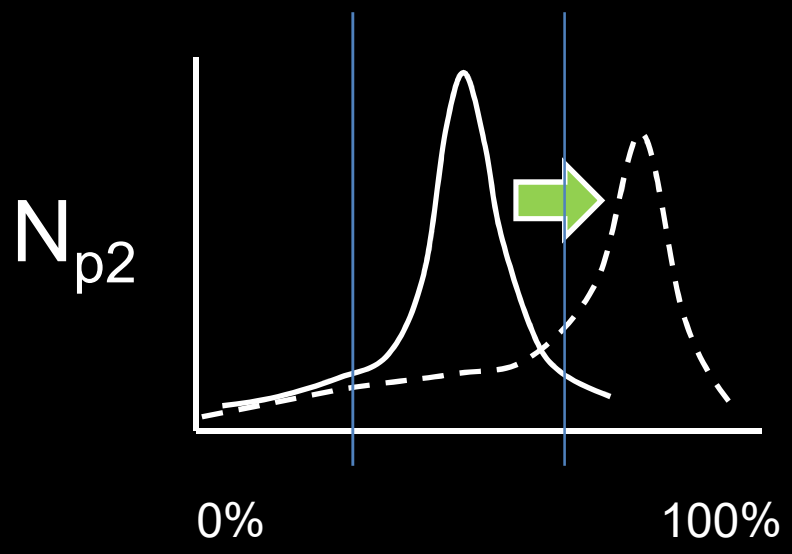
conclusions

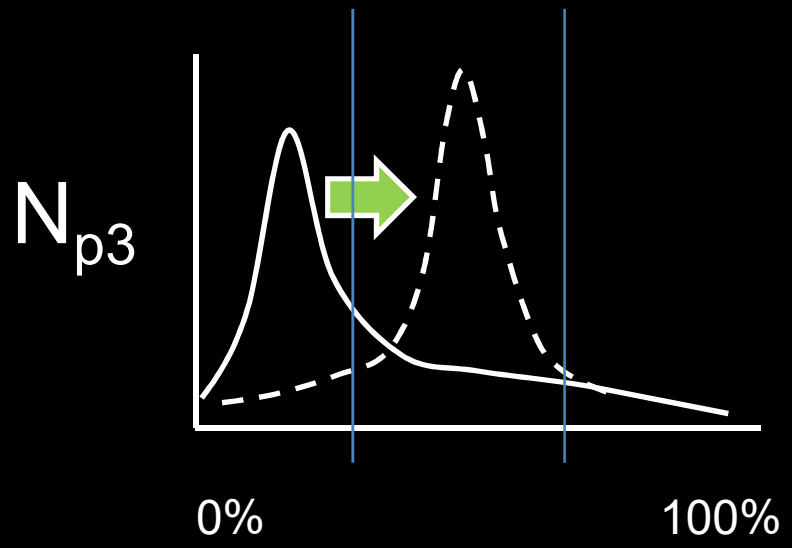

research
systems
healthcare
systems
moral
inputs
drug +
evidence
opportunity

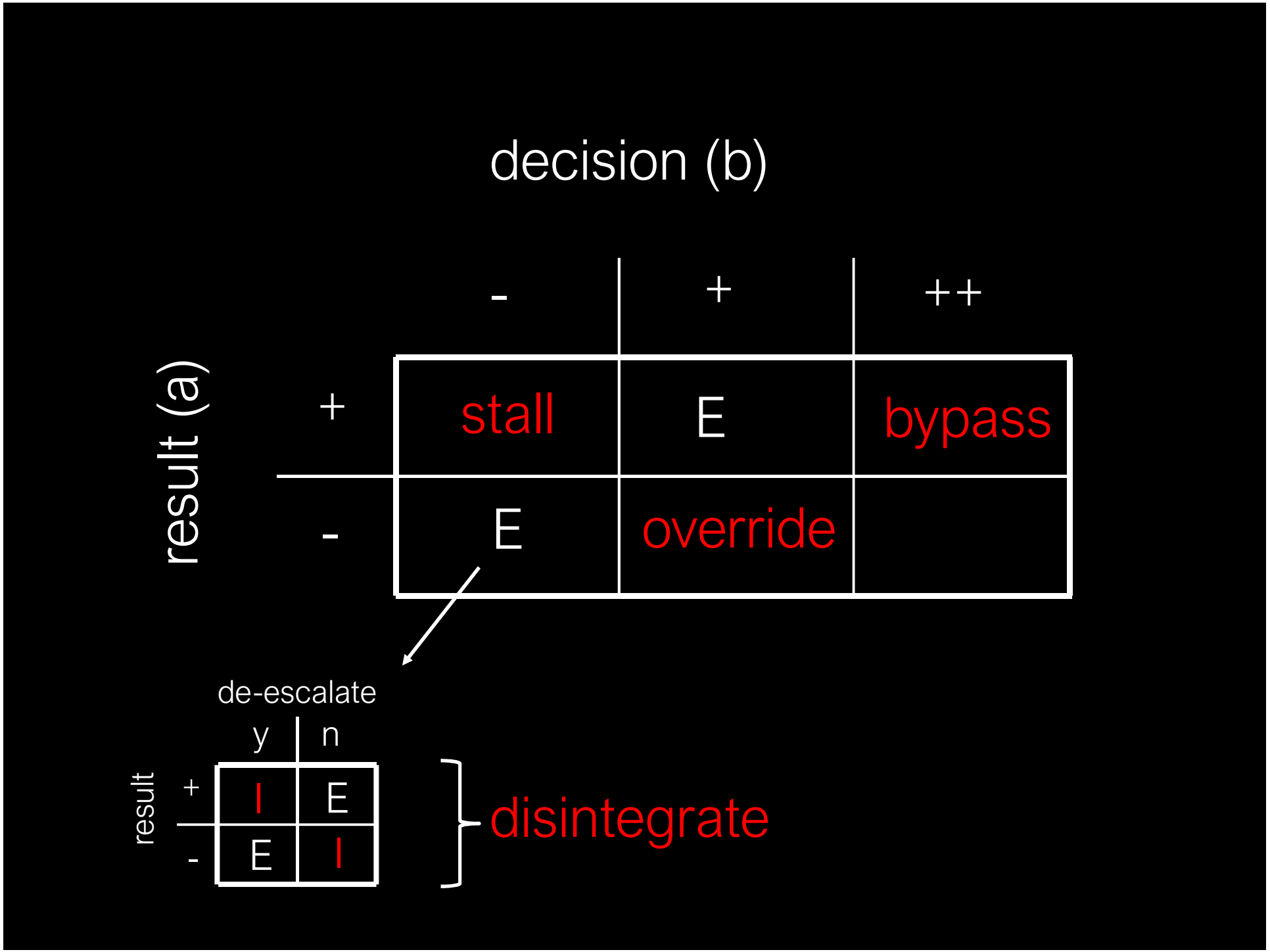

welfare
labour
opportunity
vulnerability
moral status
drug +
evidence
healthcare
systems
welfare
opportunity


threshold of action
+
N
0%
100%




N_{p2}
0%
100%


N_{p3}
0%
100%


decision (b)
-
+
++
result (a)
+
stall
E
bypass
-
E
override
de-escalate
y
n
result
+
I
E
-
E
I
disintegrate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