DANA-FARBER CANCER INSTITUTE

BRIGHAM AND WOMEN'S HOSPITAL

Harvard-MIT Center for Regulatory Science

HARVARD MEDICAL SCHOOL

GBM AGILE Platform Trial

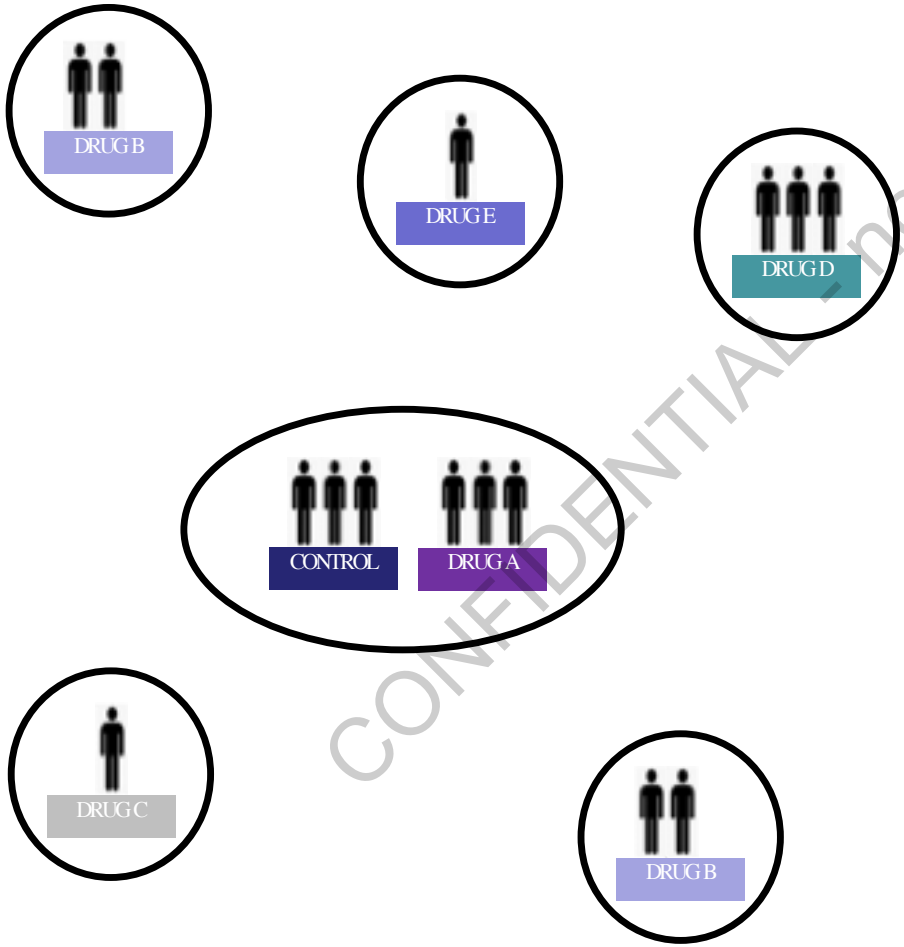
Brian Alexander, MD, MPH
NEWDIGS DESIGN LAB: LEAPS PROJECT

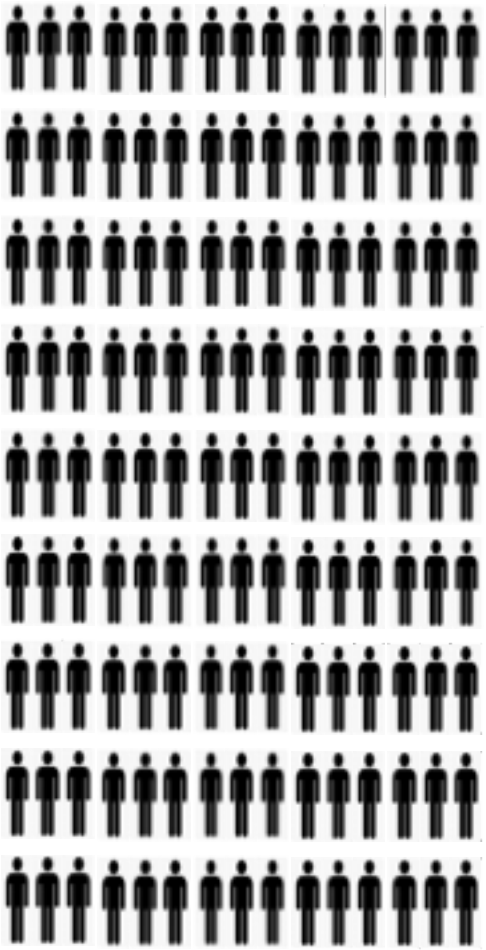
July 18, 2018

Glioblastoma

- Incurable brain tumor
  - Radiation and temozolomide "standard"
- Most patients would like to receive an experimental therapy
  - Only ~10% enroll on trials Vanderbeek et al. 2018
- Despite much research, minimal advances over decades

Clinical research ⟷ Clinical practice





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ICT-107	414*	8.92
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Nivolumab	626	–
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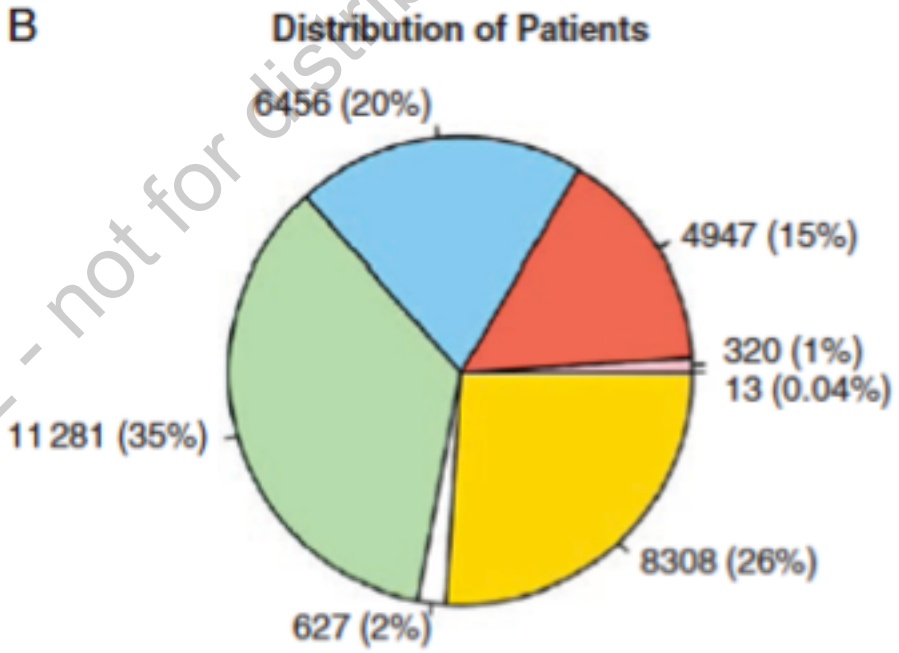
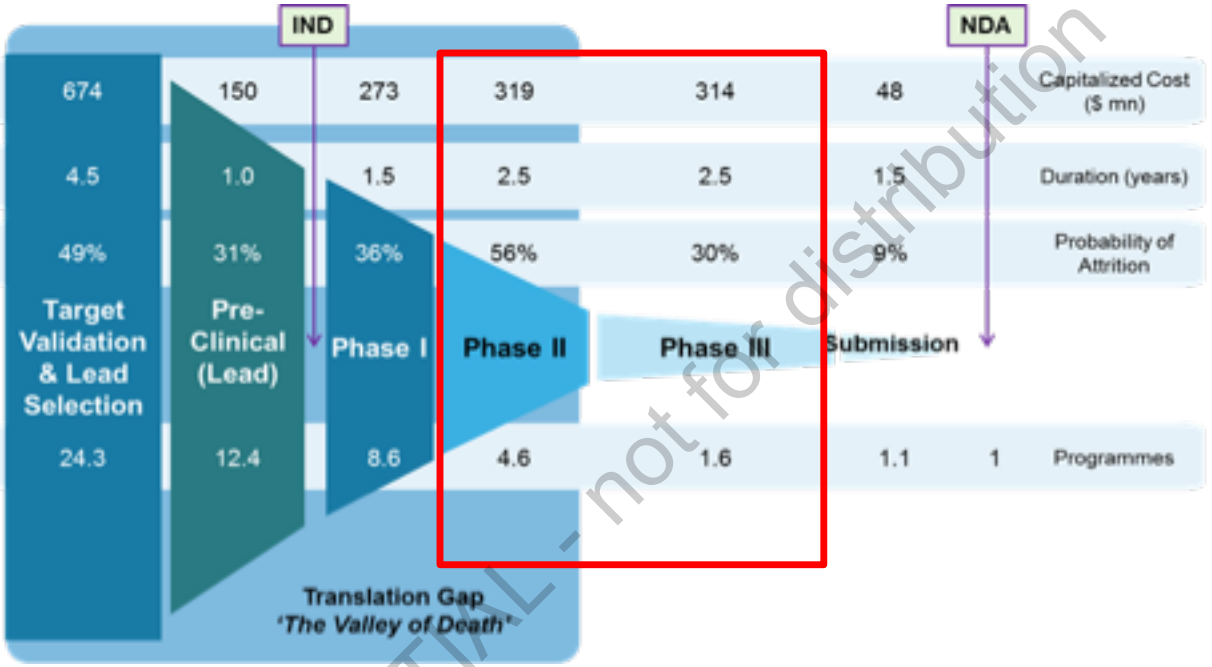
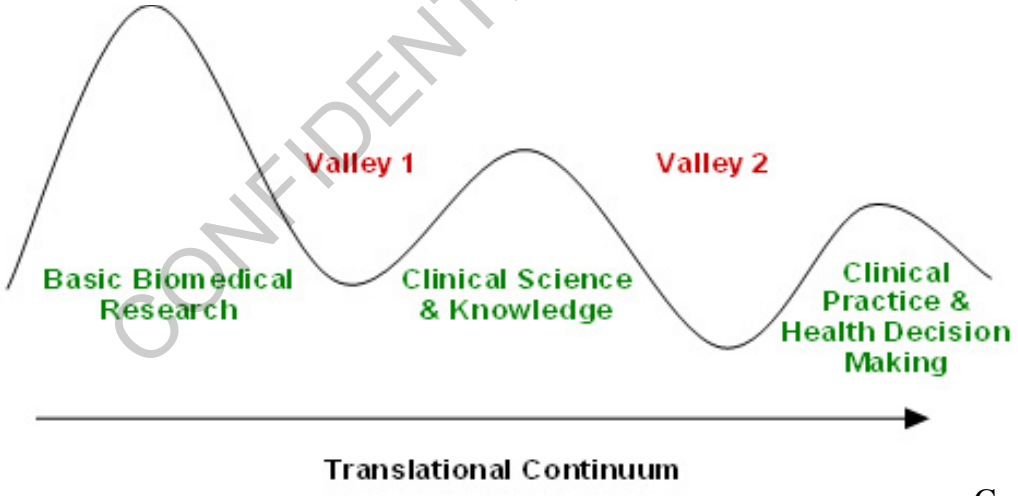
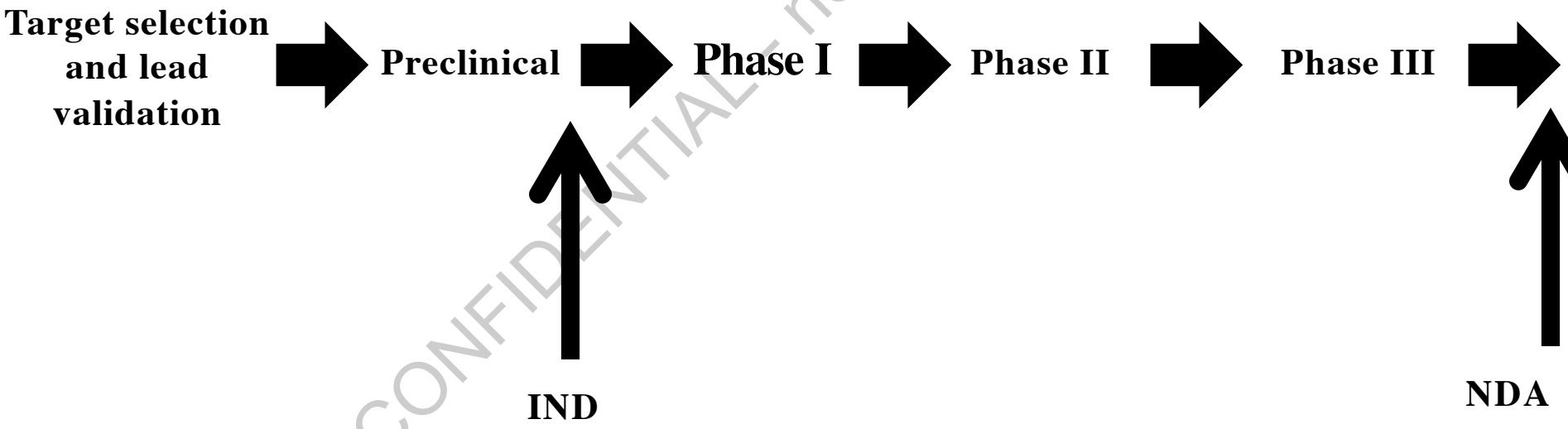
VB-111	252*	7.00

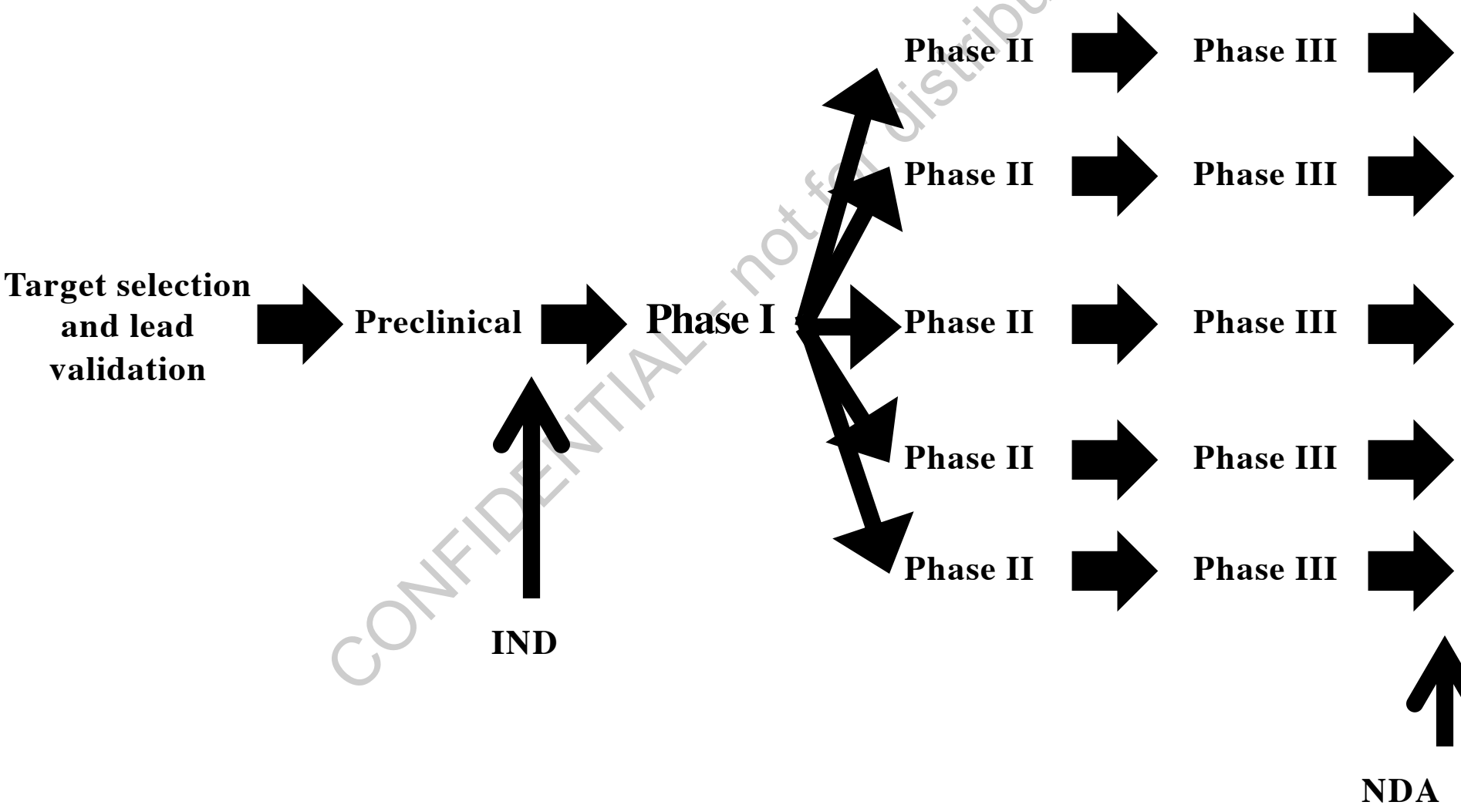


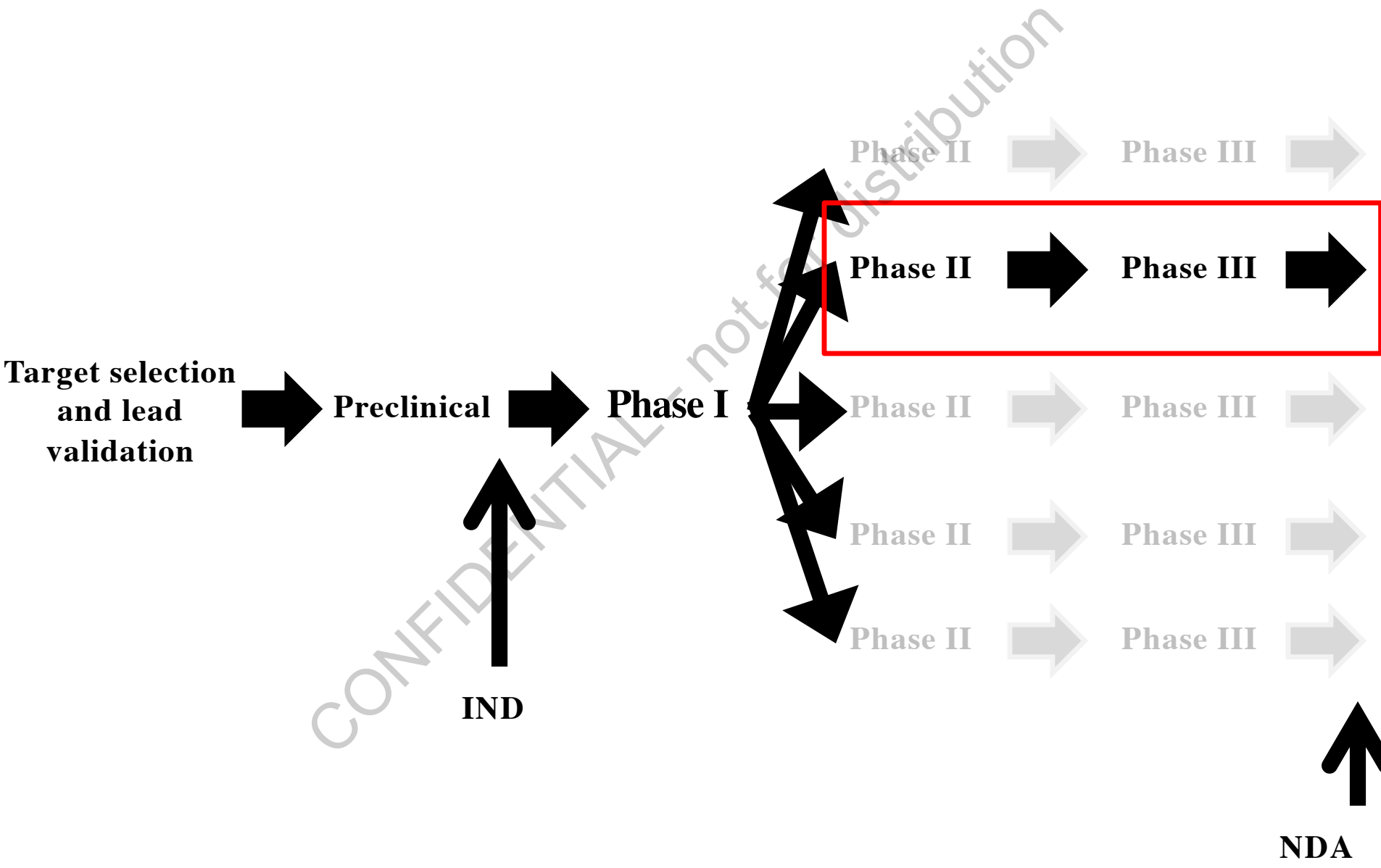
Vanderbeek et al.
Neuro Oncol 2018



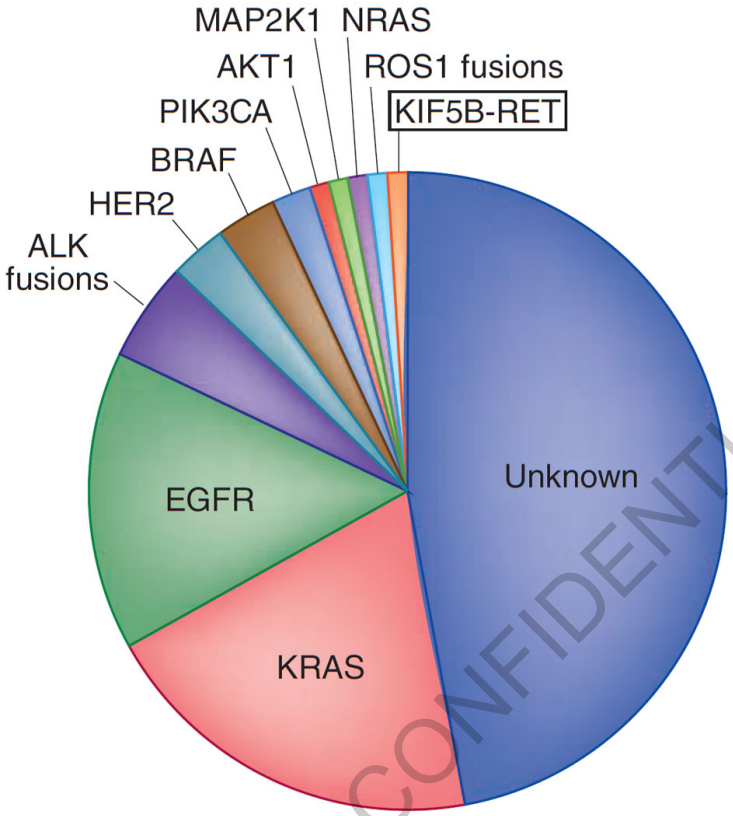




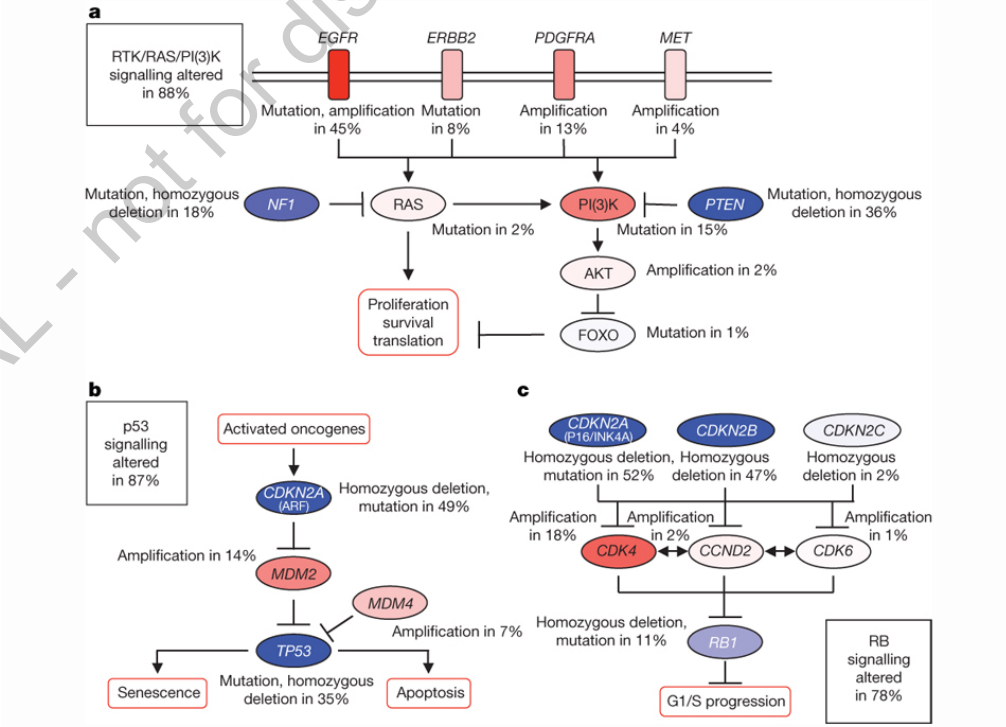




Biomarkers are different

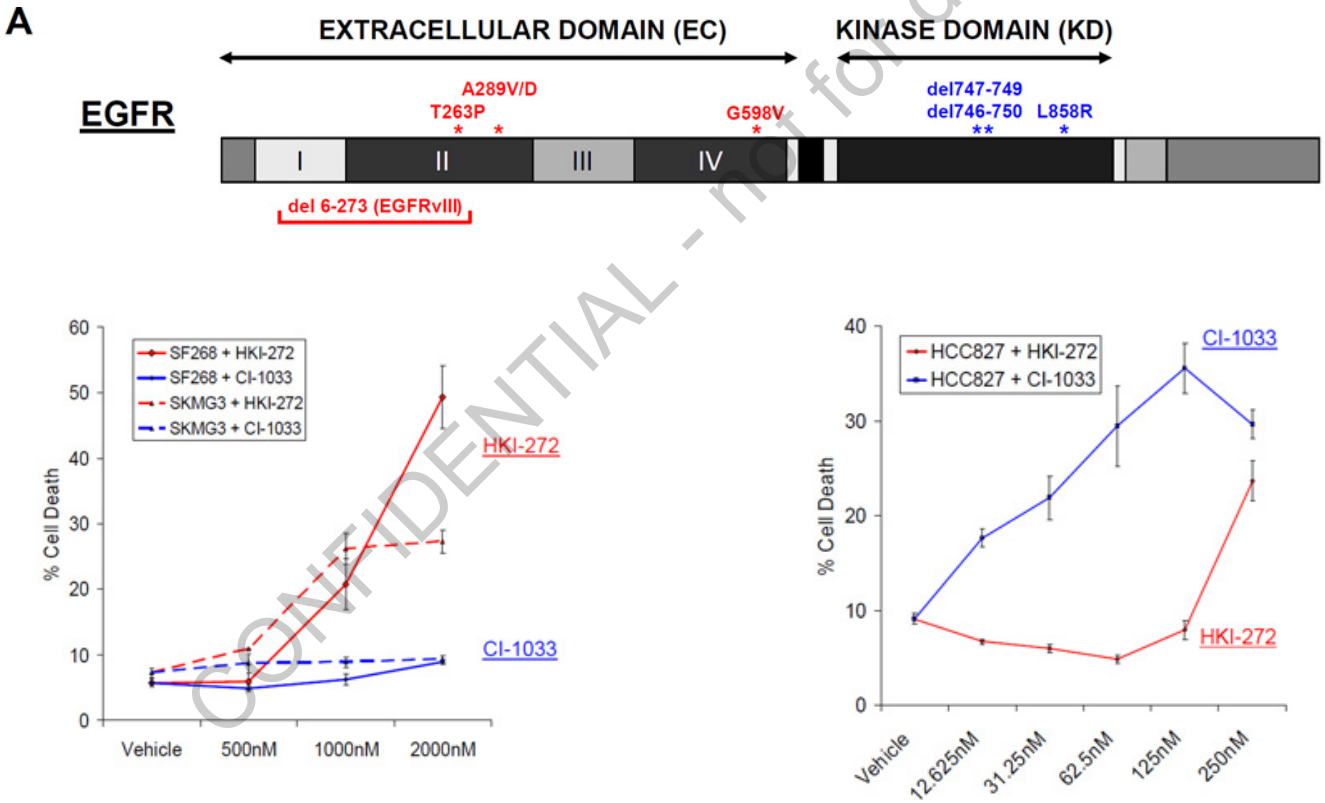


Pao and Hutchinson. *Nature Med* 2012



TCGA *Nature* 2008

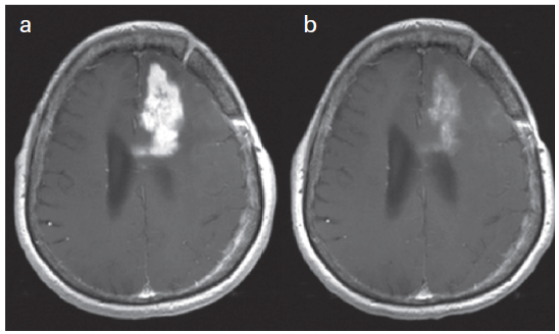
Targets are different

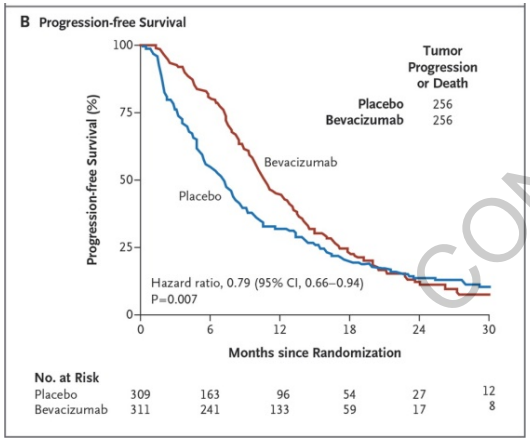


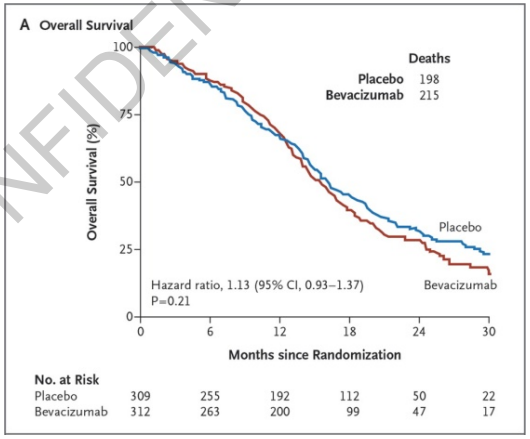
Vivanco et al. *Cancer Discov* 2012

Endpoints are different

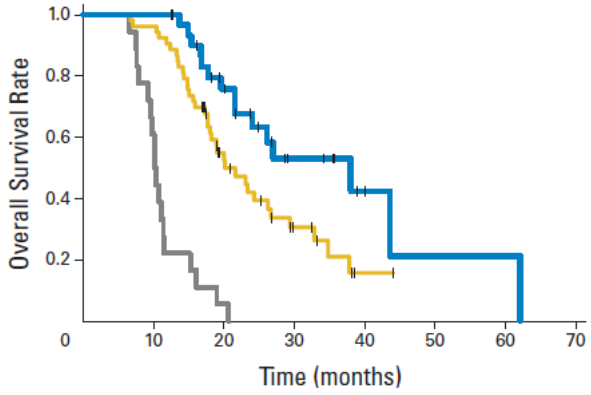
Pseudo-response







Pseudo-progression

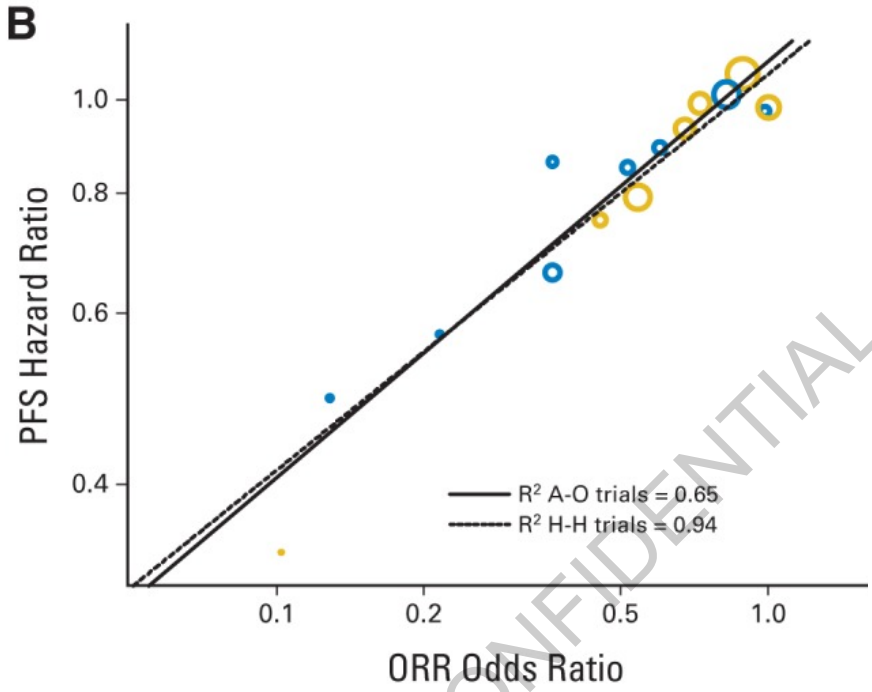


Wen et al. *J Clin Oncol* 2010

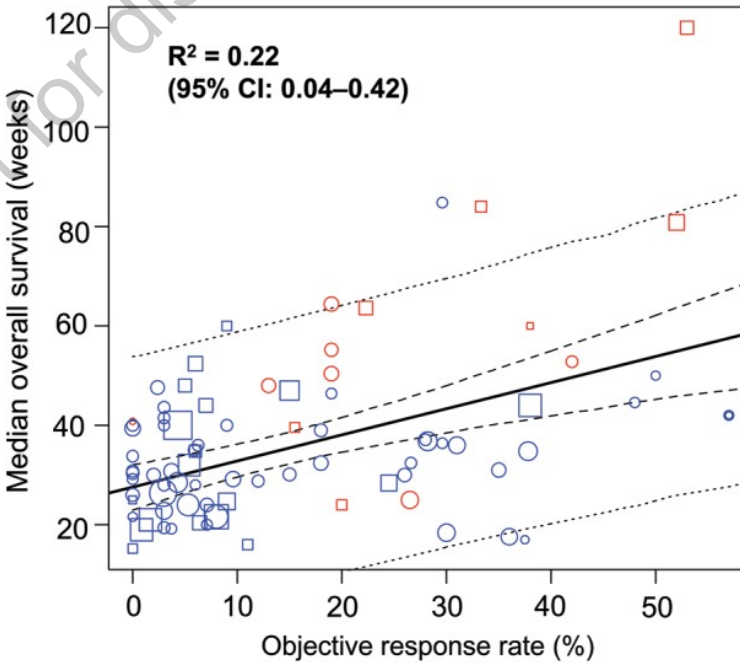
Gilbert et al. *NEJM* 2014

Brandes et al. *J Clin Oncol* 2008

Endpoints are different



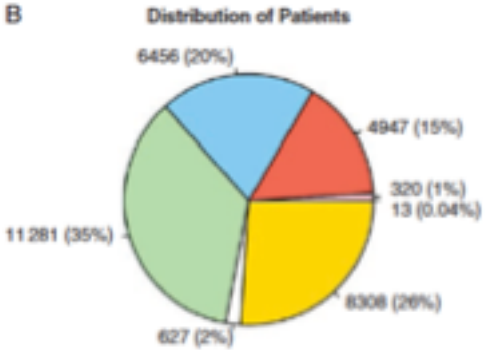
Blumenthal et al. *J Clin Oncol* 2015



Han et al. *Neuro Oncol* 2014

	N (III)	Start of Phase II to End of Phase III (years)	Preceding Phase II?	N (II)	Endpoint (II)	Randomized?
AP 12009	27	8.83	Yes	141	ORR	Yes
Bevacizumab	921	5.75	Yes	70*	OS	No
Bevacizumab	637	6.75	Yes	70*	OS	No
Cediranib	423	4.25	Yes	31	PFS	No
Cilengitide	545	7.58	Yes	112	OS	No
DCVax†	348*	9.92	Yes	240	PFS	Yes
ddTMZ	1173	–	No	–	–	–
Enzastaurin	397	4.83	Yes	120*	Anti-tumor activity	No
ICT-107	414*	8.92	Yes	124	OS	Yes
Intraoperative RT	314*	6.25	Yes	12	MTD	No
Nivolumab	626	–	No	–	–	–
Nivolumab	550*	–	No	–	–	–
NovoTTF	700*	–	No	–	–	–
NovoTTF	236	–	Yes	10	PFS/OS	No
Rindopepimut	745	9.25	Yes	82	PFS	No
VB-111	252*	7.00	Yes	75*	OS	No

B



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GBM AGILE
Adaptive Global Innovative Learning Environment

10/21/15

GBM AGILE Planning and Design Group (Overall Committee Structure)

Oversight Committee
TBD

Executive Committee
(PIs and Project Director)
Ann Barker, Sujuan Ba Mitch Berger, Don Berry, Web Cavenee, Tim Cloughesy, George Poste, and Al Yung, Mustafa Khasraw (Australia), Tao Jiang (China)

Steering Committee
(Executive Committee and Committee Co-Chairs)
Brian Alexander, Sujuan Ba, Ann Barker, Mitch Berger, Don Berry, Dan Bratt, Ken Buetow, Web Cavenee, Susan Chang, Lynda Chin, Antonio Chiocca, Tim Cloughesy, Carolyn Compton, Jason Connor, Ben Ellingson, Eva Galanis, Amy Heimberger, Jonathon Hirsch, Tao Jiang, Mustafa Khasraw, Ingo Mellinghoff, Scott Memmott, Tom Mikkelsen, Paul Mischel, George Poste, Carrie Treadwell, Catherine Stace, Laura van 't Veer, Al Yung, Xin Zhang

Clinical Trials Operations Group (CTOG)

Publications and Data Review
TBD

Final Agent Review
George Poste
Other Members
TBD

Advocacy Groups
Catherine Stace
Carrie Treadwell

Data Safety and Monitoring Board
TBD

Committees

Protocol Development
Tim Cloughesy (Chair)
Brian Alexander (Co-Chair)
Patrick Wen
Howard Colman
Paul Mischel
Jonathan Hirsch
Ingo Mellinghoff
Mustafa Khasraw
XinGuang Yu
Wenbin Li
Yu Yao
Zhenyu Zhao

Imaging
Ben Ellingson (Chair)
Eva Galanis (Co-chair)
Martin van den Bent (Co-Chair)
Whitney Pope
Sarah Nelson
Patrick Wen
Dan Sullivan
Elizabeth Gerstner
Xiang Wang
Ying Mao
Wenbin Ma
XiaoGuang Qiu

Pathology and Biospecimens
Dan Bratt (Chair)
Carolyn Compton (Co-Chair)
Xin (Vincent) Zhang (Co-Chair)
David Louis
Jason Huse
Scott VandenBerg
Xiong Ji
Michael Buckland
Xiang Wang
Michael Wang
Ping Li

Data Collection, Management – Database Development
Jonathan Hirsch (Chair)
Ken Buetow (Co-Chair)
Lynda Chin (Co-Chair)
John Quackenbush
Roeland Verhaak
Howard Colman
Ling Chen
Ying Mao
RenZhi Wang
Wei Zhang

Biomarker Selection and Development
Paul Mischel (Chair)
Laura van 't Veer (Co-Chair)
Antonio Chiocca (Co-Chair)
Steve Gutman
Michael Prados
Michael Weller
David Ashley
Hai Yan
Federico Goodsaid
Ben Ellingson
Tao Jiang
Qing Mao
Ling Chen
James Heath

Target Identification And Agent Selection
Amy Heimberger (Chair)
Ingo Mellinghoff (Co-Chair)
Tom Mikkelsen (Co-Chair)
John Sampson
Cameron Brennan
Lewis Cantley
John de Groot
Howard Fine
RenZhi Wang
Qing Mao
Tao Jiang

Trial Design
Don Berry (Chair)
Brian Alexander (Co-Chair)
Jason Connor (Co-Chair)
Susan Chang (Co-Chair)
Lisa LaVange
Rajeshwa Sridhara
Wolfgang Wick
Linda Liau
Mustafa Khasraw
Mark Rosenthal
Wenbin Li
Kun He
Xinguang Yu
Xinghe Wang

Advocacy - Communication
Carrie Treadwell (Co-Chair)
Catherine Stace (Co-Chair)
Max Wallace (Co-Chair)

Additional Members to be Named

International Coordination
Michelle Stewart (Co-Chair)
Sujan Ba (Co-Chair)
Wolfgang Wick (Co-Chair)
Mustafa Khasraw (Co-Chair)
Wolfgang Wick
Rajeshwari Sridhara
Ying Mao

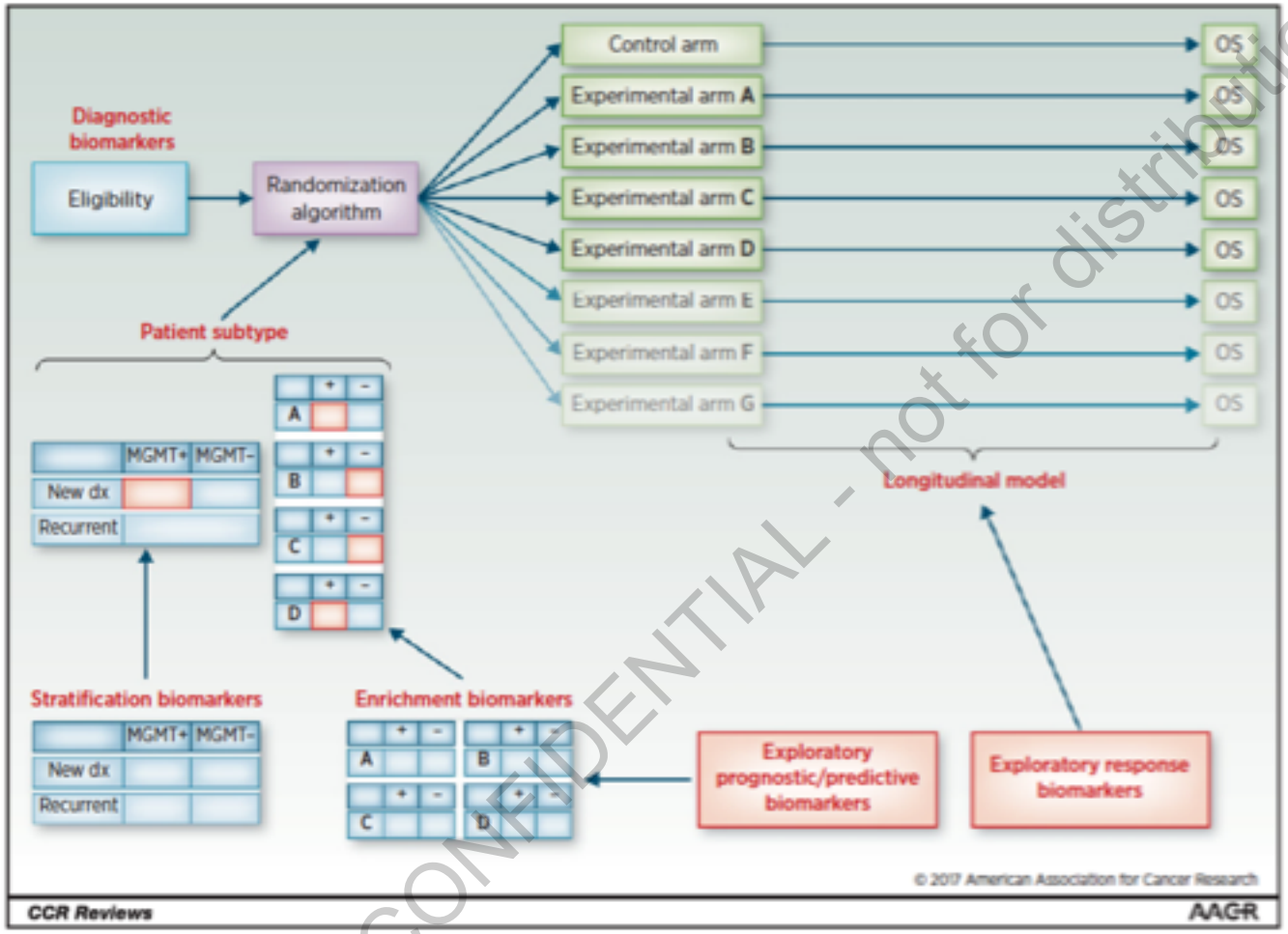
Platform trial for GBM

- Create one trial infrastructure
  - Common biomarker, endpoint evaluations
  - Add/drop arms as trial is ongoing
  - Preserves indication-specific knowledge
- Replace serial trials
  - Eliminate "downtime"
  - Avoid "recreating the wheel"
- Ongoing concern to provide incentives for proactive therapeutic identification

GBM Development is different than other cancers

- Imaging-based endpoints can be misleading — Use OS
- Historical control comparison can under- and overestimate treatment effect leading to bad decisions — Use controls
- Different targets, different biomarkers for similar pathways — GBM-specific agents
- Biomarker subgroups are not well defined — Multiplex markers, learn in trial
  - Overlapping genomic groups
  - No gold standard for MGMT

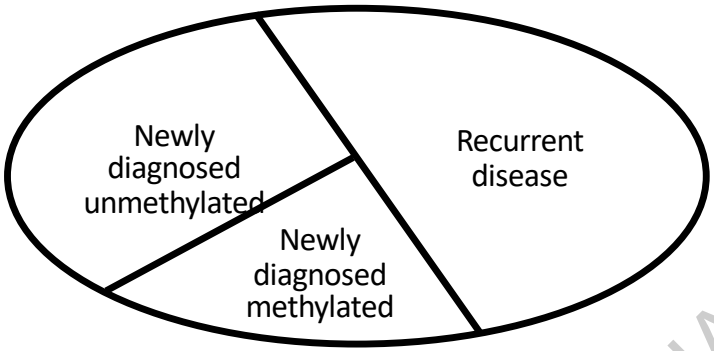
GBM AGILE



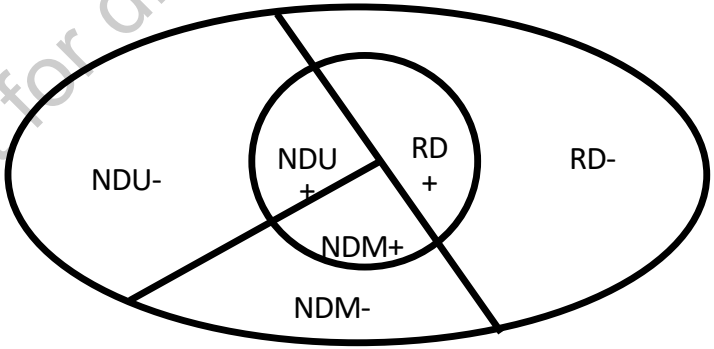
GBM AGILE
Adaptive Global Innovative Learning Environment

Subtype

- Characteristic of the patient/tumor
- Partitions the biomarker space
- Where randomization probabilities can vary



Subtypes with Stratification Biomarkers Only



Subtypes with Enrichment Biomarkers

Signature

- Characteristic of the experimental therapy
- Can be overlapping
- Best indication for further development

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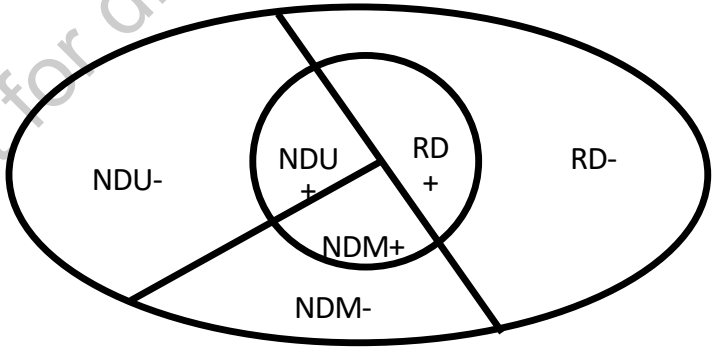

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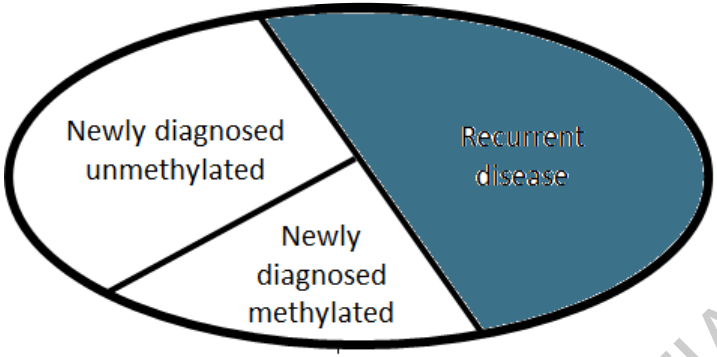

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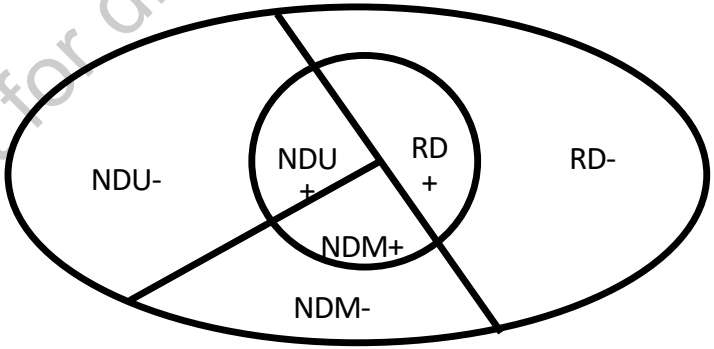

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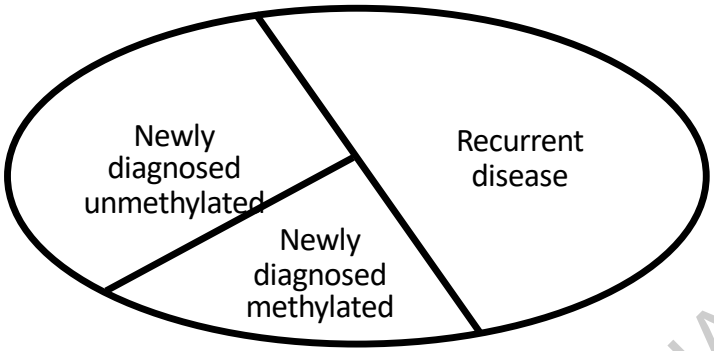

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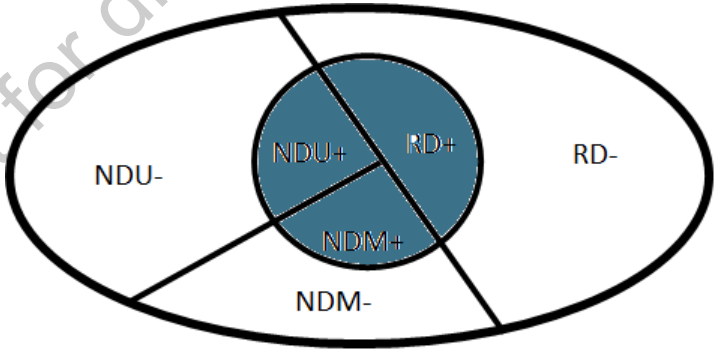

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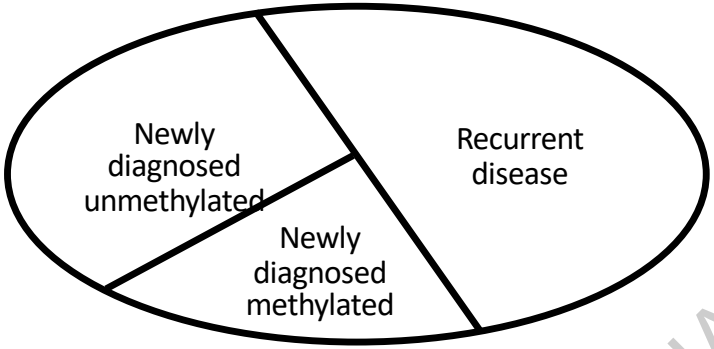

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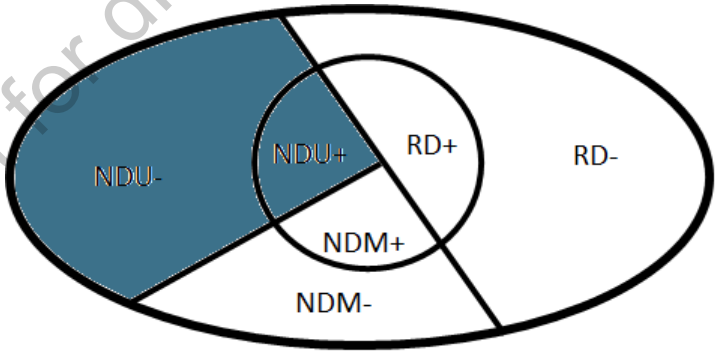

Subtypes with Enrichment Biomarkers

Advantages of GBM AGILE for Drug Development

- GBM AGILE platform
  - Regulatory buy-in
  - Access to diverse group of experts in the field, operational expertise enabling trial to evolve with success
  - Common infrastructure: harmonization of imaging, tissue acquisition, trial data
- Cost - commercial grade development vehicle at reduced Phase II/III pricing
  - Efficiencies in patient utilizations: common controls, adaptive randomization
  - Right-sized" (# of patients = outcome of utility)

GBM AGILE

Advantages of GBM AGILE for Drug Development

- Speed
  - Accelerates time from “hand shake” to arm initiation to last patient out
  - “Seamless” transition to Phase III, Phase II patients are used in final analysis
- Defines subsets of patients most likely to benefit from therapy
- Can incorporate predictive biomarkers (hypothesis testing and generating)
- *Forms the foundation for future combinations through the time machine/non-concurrent controls

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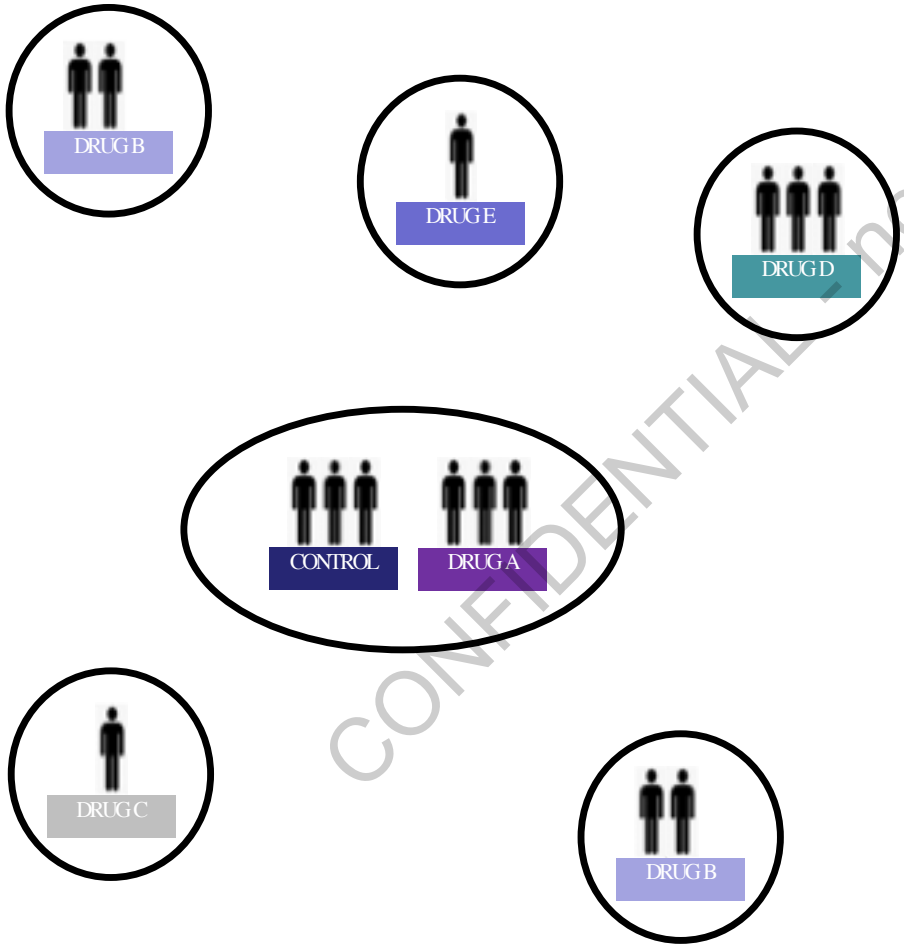
REV. JANUARY 18, 2018

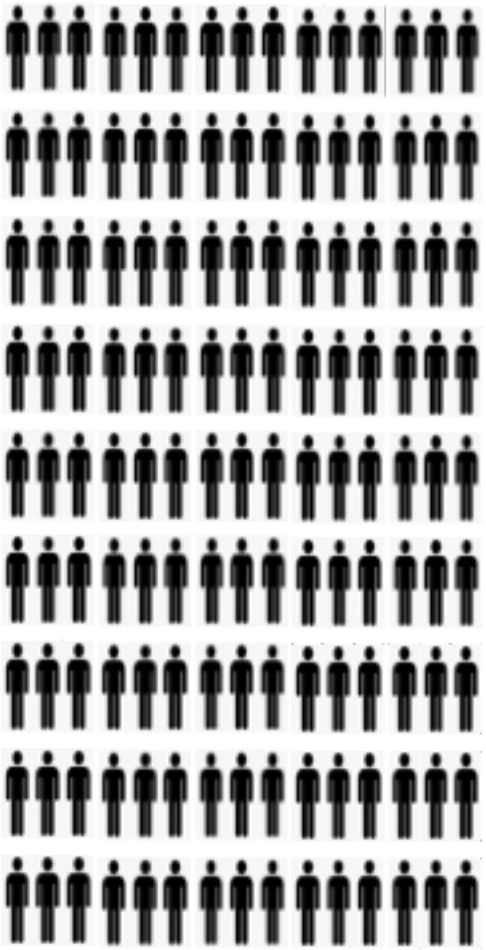
ARIEL D. STERN

SARAH MEHTA

Adaptive Platform Trials: The Clinical Trial of the Future?

Clinical research ⟷ Clinical practice

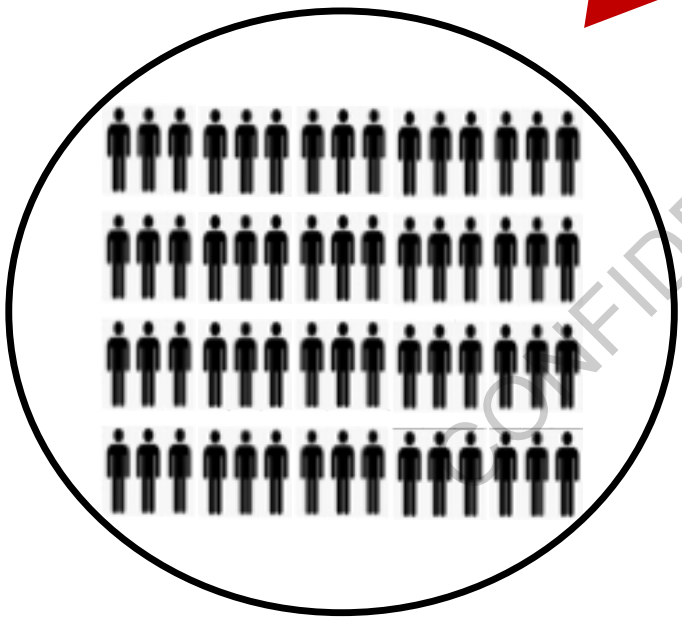


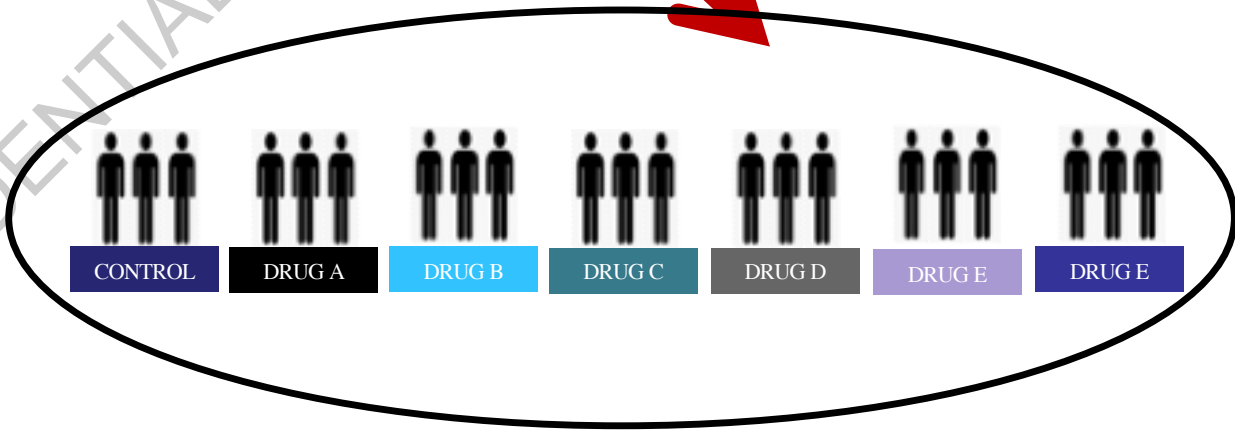


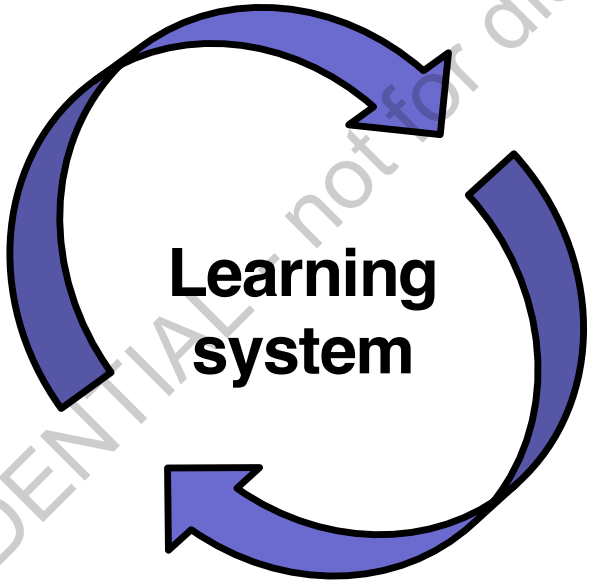
Clinical practice ⟷ **Clinical research**

"Real world evidence"

Adaptive platform trials







Patients

Doctors

Payers

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