



CRAFTSMANSHIP IN PHARMACEUTICAL PORTFOLIO MANAGEMENT

A quantitative approach to making better decisions for
Pharma Companies and society

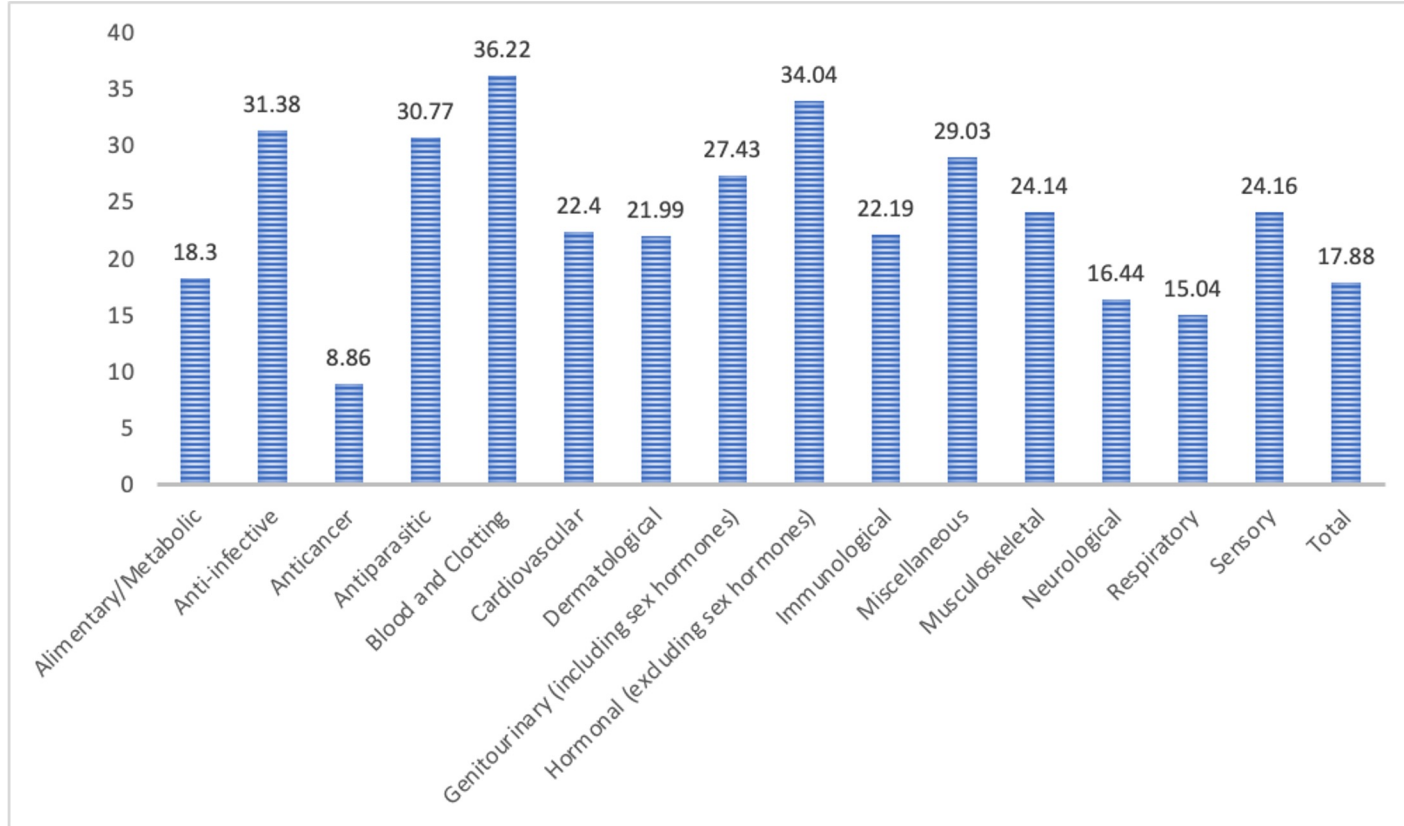
HENRY J. CONTER, BESC, MD, MSF, MSC, FRCPC
PORTFOLIO MANAGER & MEDICAL DIRECTOR, PHARMA RESEARCH AND
EARLY DEVELOPMENT
HOFFMAN-LA ROCHE, BASEL SWITZERLAND

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PROBABILITY OF SUCCESS VARIES ACROSS

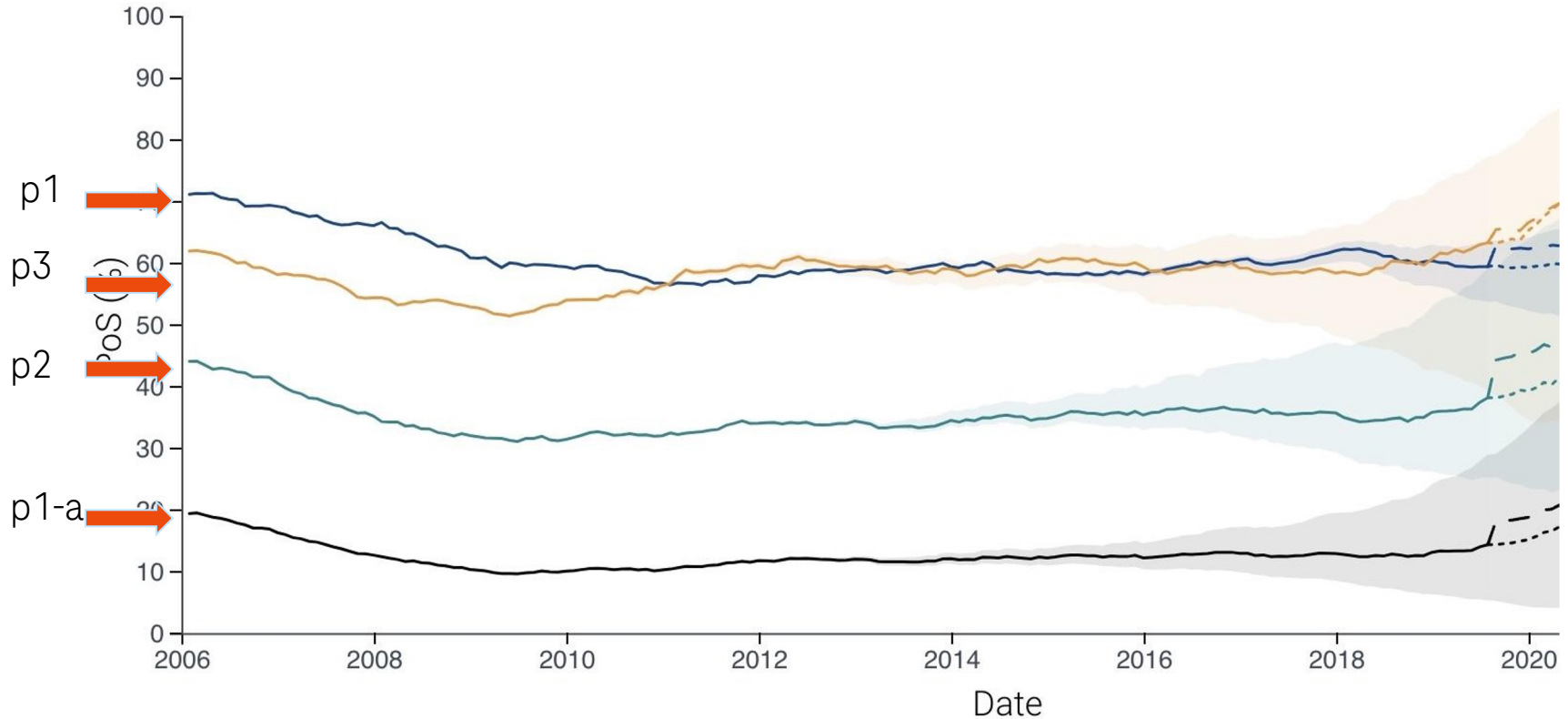
INDICATIONS

OUR ABILITY TO SUCCESSFULLY TRANSLATE SCIENTIFIC KNOWLEDGE INTO NEW PHARMACEUTICALS



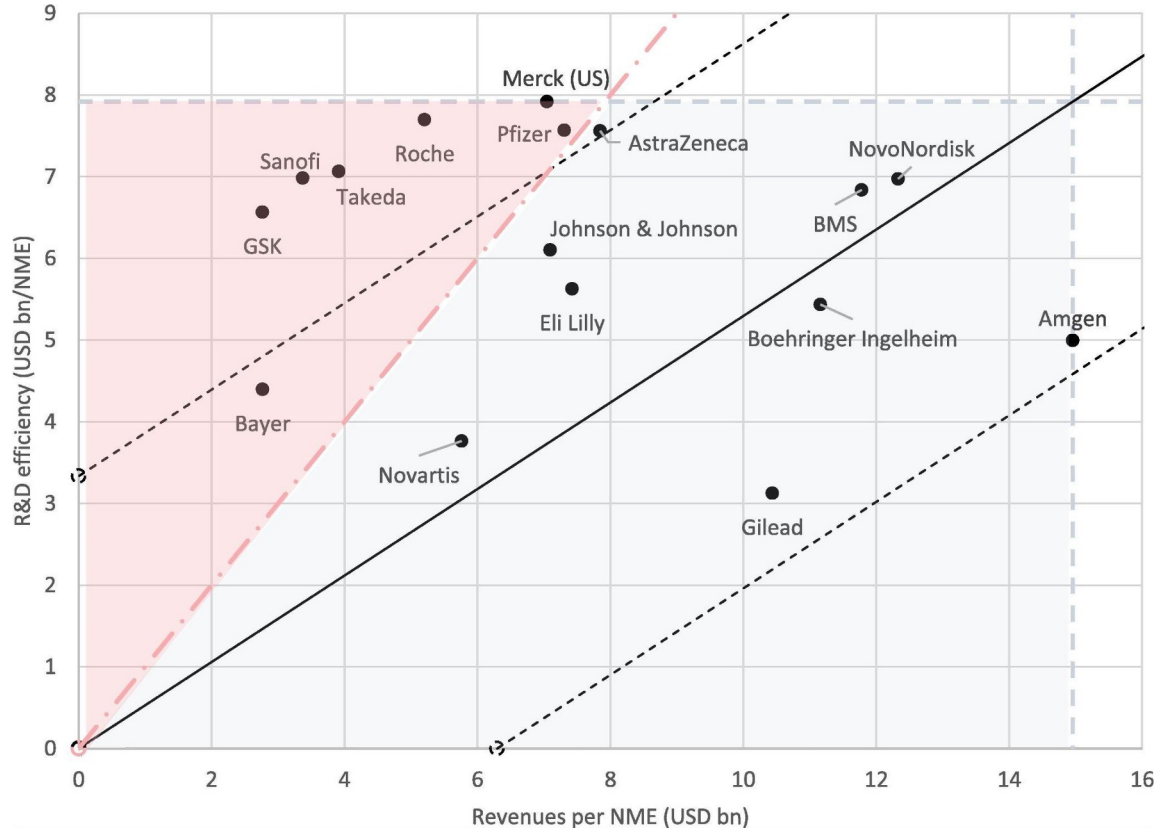
CLINICAL TRIAL SUCCESS RATES ARE FLAT

POS RATES, 3 YEAR ROLLING WINDOW ACROSS ALL DISEASE AREAS 2006-2020



NEGATIVE PHARMA R&D PRODUCTIVITY IS COMMON

AVERAGE R&D EXPENDITURE = \$6.16B FROM 2001-2020 (CAGR=6%)

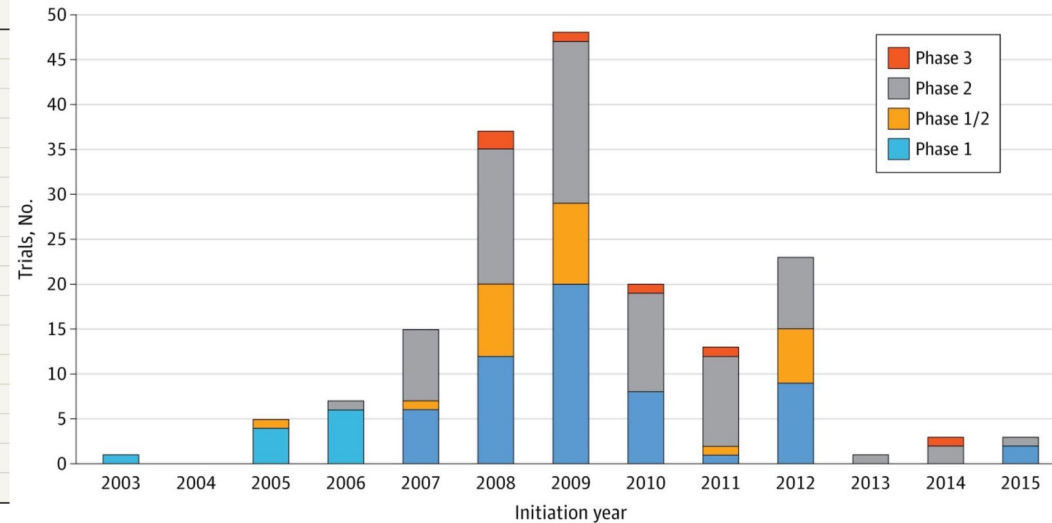


IGF1-R inhibitors as a case study in pharma concentration

\$1.6B USD lost for 16 drugs, 183 trials, >12,000 patients

Drug name	IGF-1R inhibitor type	Company	Estimated No. of patients
AMG479 (ganitumab)	Antibody	Amgen/NantCell	2864
AVE1642	Antibody	Sanofi-Aventis	57
AXL1717	Small molecule	Axelar AB	204
BIIB022	Antibody	Biogen Idec	98
BMS-754807	Small molecule	Bristol-Myers Squibb	296
CP-751 871 (figitumumab)	Antibody	Pfizer	2029
IGV-001	Antisense/cell therapy	Imvax	93
IMCA12 (cixutumumab)	Antibody	Eli Lilly and Company/NCI	2791
KW-2450	Small molecule	Kyowa Hakko Kirin Pharma Inc	83
MK7454 (robatumumab)	Antibody	Merck & Co/Schering Plough	305
MK0646 (dalotuzumab)	Antibody	Merck, Sharpe & Dohme Corp	1436
MM141 (istiratumab)	Antibody	Merrimack Pharmaceuticals	135
OSI906 (linsitinib)	Small molecule	Oncogene Sciences/Astellas Pharma Inc	1277
PL225B	Small molecule	Piramal Enterprises Ltd	70
RG1507 (teprotumumab)	Antibody	Hoffmann-La Roche	525 ^b
XL228	Small molecule	Exelixis	133

A Clinical trials distinguished by phase



TWO WAYS TO FIX THIS PROBLEM:

BETTER MOLECULE DECISION-MAKING, BETTER PORTFOLIO DECISION-MAKING

MOLECULE DECISION-MAKING:

1. FUNDAMENTAL DISEASE KNOWLEDGE.
1. IMPROVED MOLECULE DESIGN.
1. STATISTICAL POST TRIAL ANALYSIS.
 - a. QUANTITATIVE

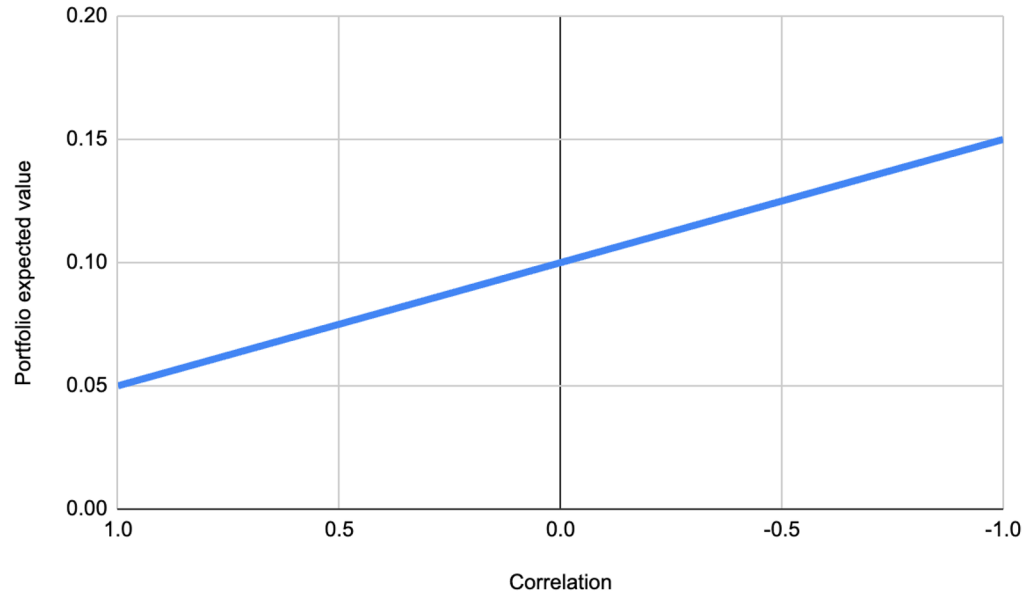
PORTFOLIO DECISION-MAKING:

1. CUSTOM REFERENCE CLASS FORECASTING.
- 1. DIVERSIFICATION.**
1. RISK TARGETING.

WHAT DOES DIVERSIFICATION DO?

DIVERSIFICATION AND PORTFOLIO VALUE

- Development program A, 95% fail
 - Development program B, 95% fail
1. Value of portfolio AB if 100% correlated?
 - a. **$=0.05 + 0.05 - 0.05 = 0.05$**
 1. What if there is no correlation?
 - a. **$=0.05+0.05 - 0 = 0.1$**
 1. What if there is perfect -ve correlation?
 - a. **$=0.05+0.05 - (-0.05) = 0.15$**



DIVERSIFICATION ENABLES RISK-TAKING

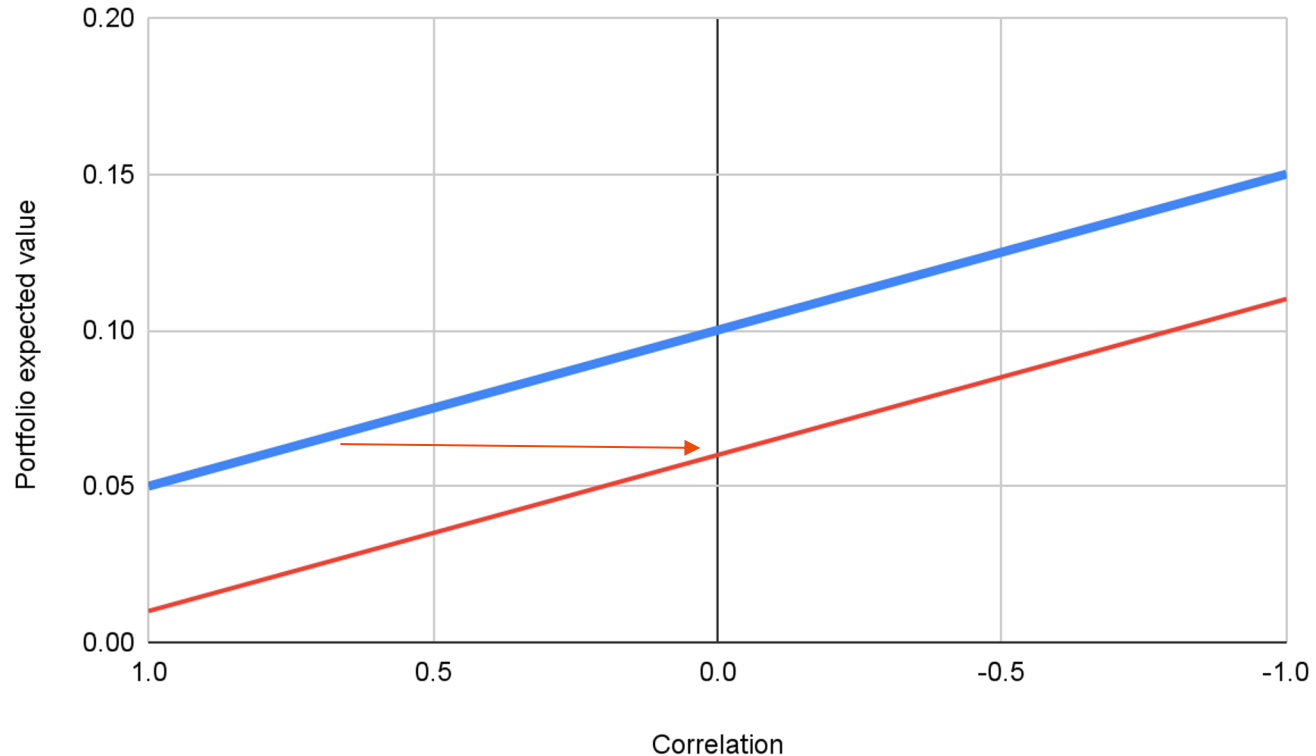
DIVERSIFICATION INCREASES PORTFOLIO VALUE

- Portfolio 1:
 - A=B=95% fail
- Portfolio 2:
 - A=95%
 - B=99% fail

Portfolio 1 @ 0.79 cor

=

Portfolio 2 @ 0 cor



HOW CAN WE ESTIMATE RELATIONSHIP?

MOLECULE DIVERSITY VS. PORTFOLIO OUTCOMES

MOLECULE DIVERSITY: VECTOR CREATION

	Mechanism			Technology			Formulation		Toxicity		
	M1	M2	M3	Mab	Vaccine	Small Mol	IV	oral	T1	T2	T3
product 1	1	0	0	1	0	0	1	0	1	1	0
product 2	1	0	0	1	0	0	1	0	0	1	0
product 3	0	1	0	0	1	0	1	0	1	0	1
product 4	0	0	1	0	0	1	0	1	0	1	1
product 5	1	0	0	1	0	0	0	0	0	0	0

$$d(x,y) = x.y / ((|x|*|x|) + (|y|*|y|) - x.y)$$

PORTFOLIO OUTCOMES: SUCCESS AS RETURNS

1. SUCCESS RATES.
1. CORRELATION.
1. COVARIANCE.

MOLECULE ASSESSMENT IN DIVERSIFICATION

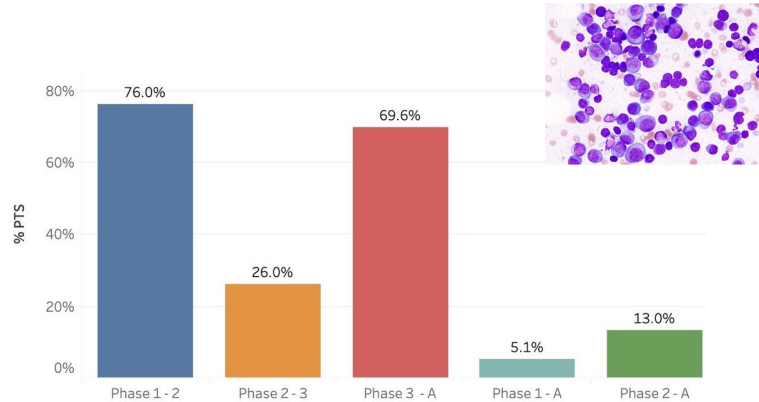
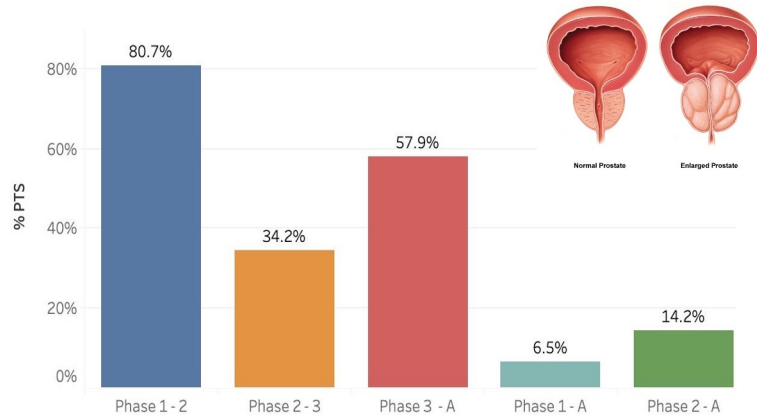
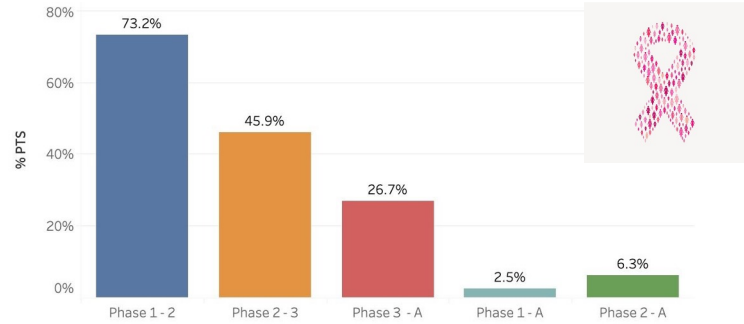
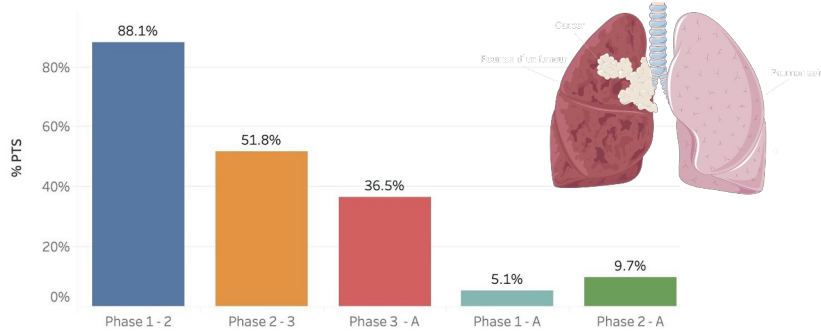
ACROSS CLASS COMPARISON VS IN-CLASS COMPARISON

	TKI	ADC	Cytotoxic	GT	DDR	CPI
TKI	1	X	X	X	X	X
ADC	0.15	1	X	X	X	X
Cytotoxic	0.15	0.17	1	X	X	X
GeneTX	0.08	0.13	0.22	1	X	X
DDR	0.28	0.16	0.24	0.15	1	X
CPI	0.16	0.18	0.19	0.29	0.14	1

	veliparib	olaparib	atezolizumab	pembrolizumab	nivolumab
veliparib	1.00	X	X	X	X
olaparib	0.67	1.00	X	X	X
atezolizumab	0.11	0.14	1.00	X	X
pembrolizumab	0.11	0.19	0.67	1.00	X
nivolumab	0.10	0.17	0.80	0.87	1.00

SUCCESS/FAILURE HINT AT ABILITY + KNOWLEDGE

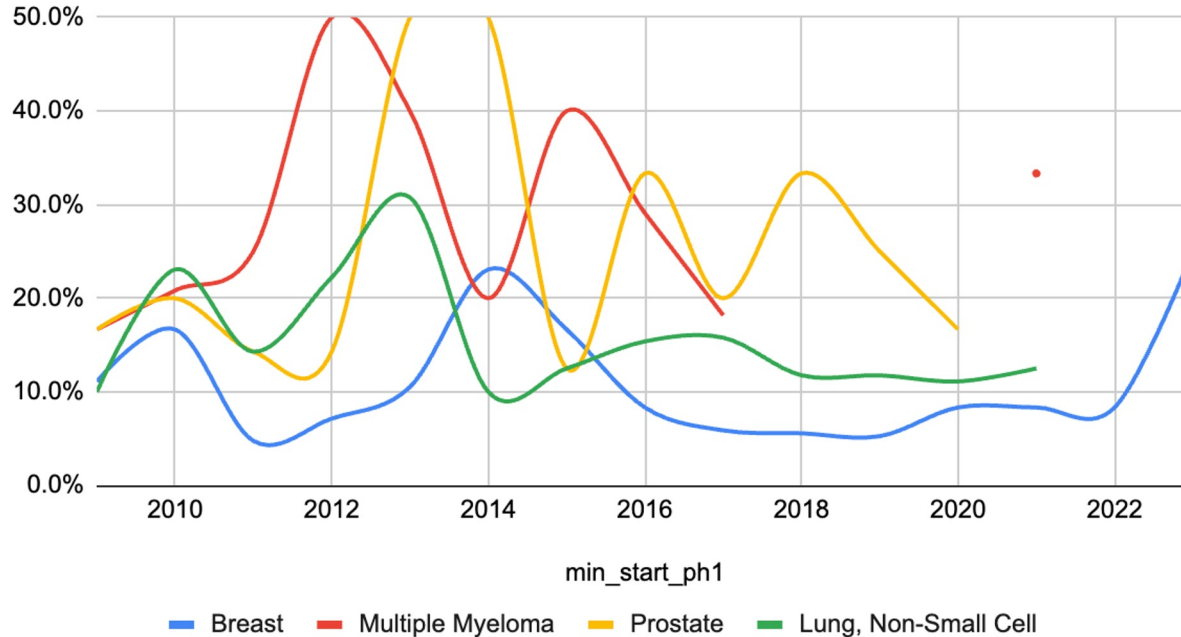
DIFFERENT DISEASES ARE BETTER OR WORSE UNDERSTOOD



PROBABILITIES CHANGE FREQUENTLY

LEADS TO BOOM+BUST CYCLES

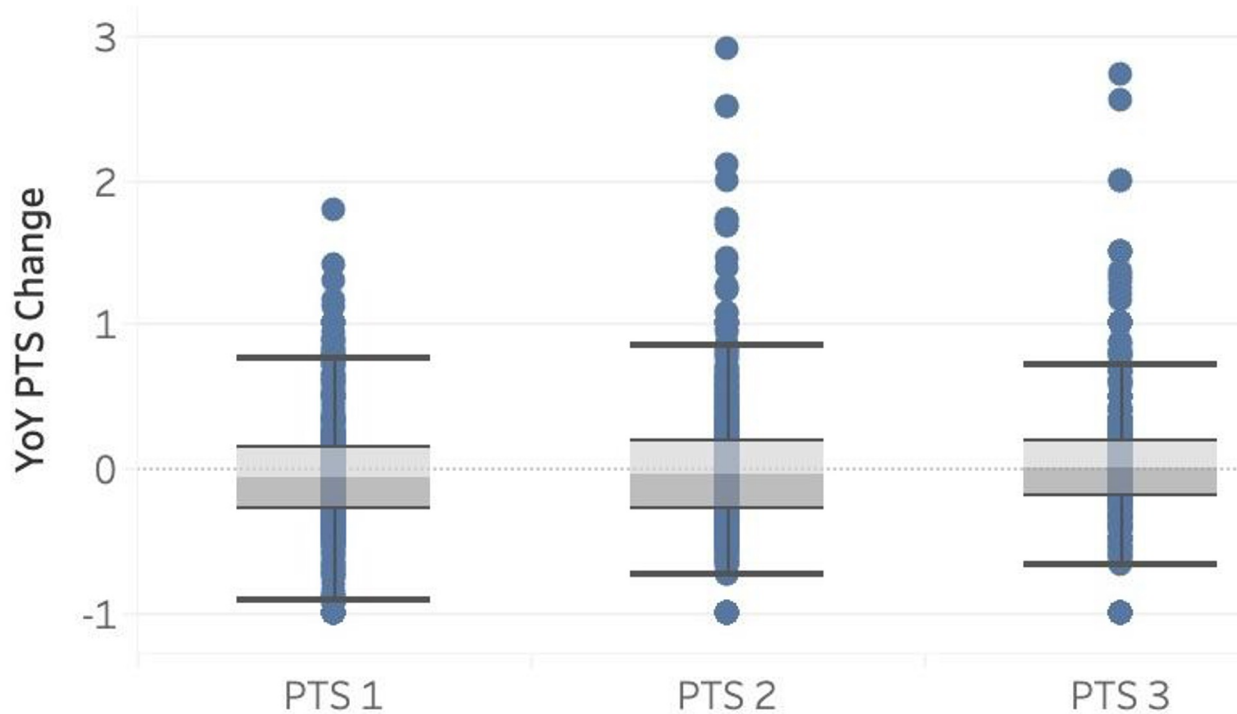
Probability 1-Approval Transition



REALIZED PORTFOLIO OUTCOMES, REALIZED DIVERSITY

PTS CHANGES YEAR OVER YEAR

PTS Volatility



DIVERSIFICATION REDUCES VARIANCE OF OUTCOMES

THE WHOLE IS GREATER THAN THE SUM OF ITS PARTS!

- 1. LUNG:
 - a. PTS = 5%, STD = 47%

- 1. CLL:
 - a. PTS = 5%, STD = 36%

- 1. COLON:
 - a. PTS = 1%, STD = 46%

- 1. **EQUAL WEIGHT L-C-C:**
 - a. **PTS = 4%, STD: 21%**

Portfolio Variance Formula



$$\text{Variance} = (w(1)^2 \times o(1)^2) + (w(2)^2 \times o(2)^2) + (2 \times (w(1) \times o(1) \times w(2) \times o(2) \times q(1,2)))$$

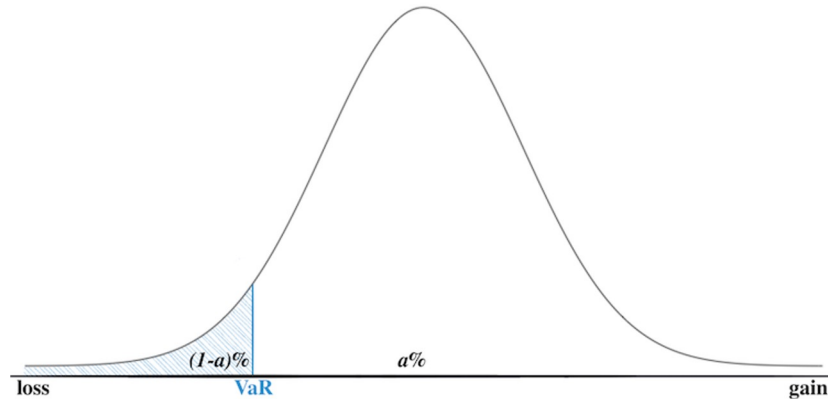


PORTFOLIO PATHS & VALUE @ RISK

WHAT ARE THE CHANCES OF A BAD OUTCOME?

What is Value At Risk?

Chance of a pre-specified loss, over a specific time.



Why should I care?

We invest in compounds with specific objectives in mind

1. Chance of approval.
2. Revenue post approval.

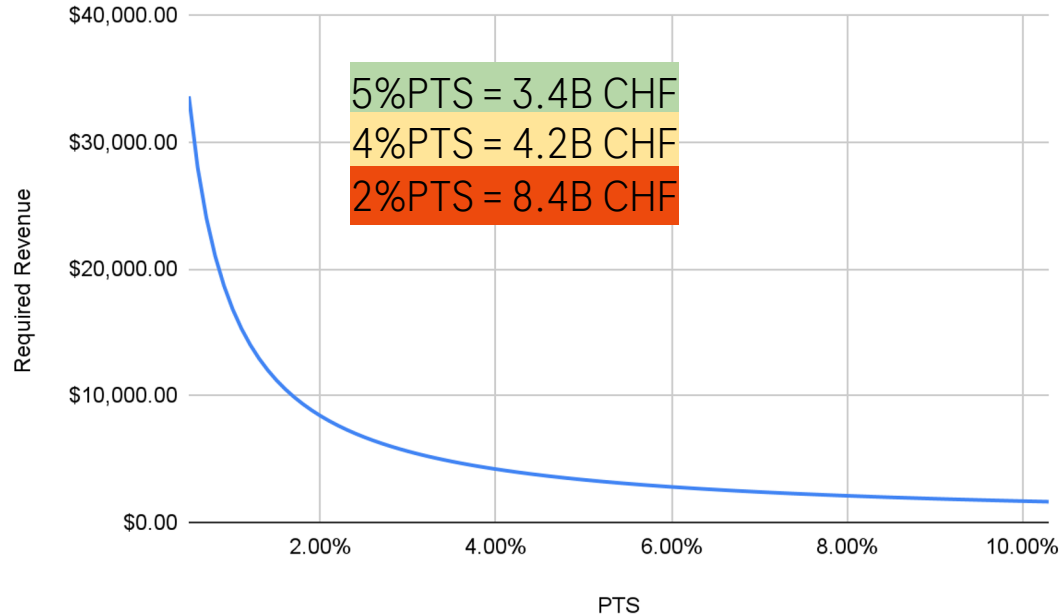
A company under performing either of these, will fail in the long run.

DIVERSIFICATION REDUCES VALUE @ RISK

WHAT ARE THE CHANCES OF REALIZING A PTS OF 2% OR LESS?

LUNG: PTS = 5%, STD = 47% (NNT 20)

3x Diversified: PTS = 4%, STD = 21% (NNT 25)



VAR < 2% PTS = 10% chance

VAR < 2% PTS = 1% chance

Summary

1. Biopharma has a R&D productivity problem.
2. Quantification of diversity:
 - a. increases the amount of risk a company can take.
 - b. reduces boom-bust cycles.
 - c. reduces catastrophic outcomes.

Doing now what patients need next