Balancing discovery and implementation in eMERGE

Points

- Discovery in clinical trials vs discovery in EMRs
  - eMERGE EMRs is a fantastic discovery resource
  - May take more resources to fully utilize
- Can you implement if you don’t know if it works?

Topo II inhibitor-Induced AML

- ~ uniformly fatal
- Etoposide/teniposide>anthracyclines
- short onset (< 3 years)
- cumulative incidence 1-20%
- ? related to cumulative dose

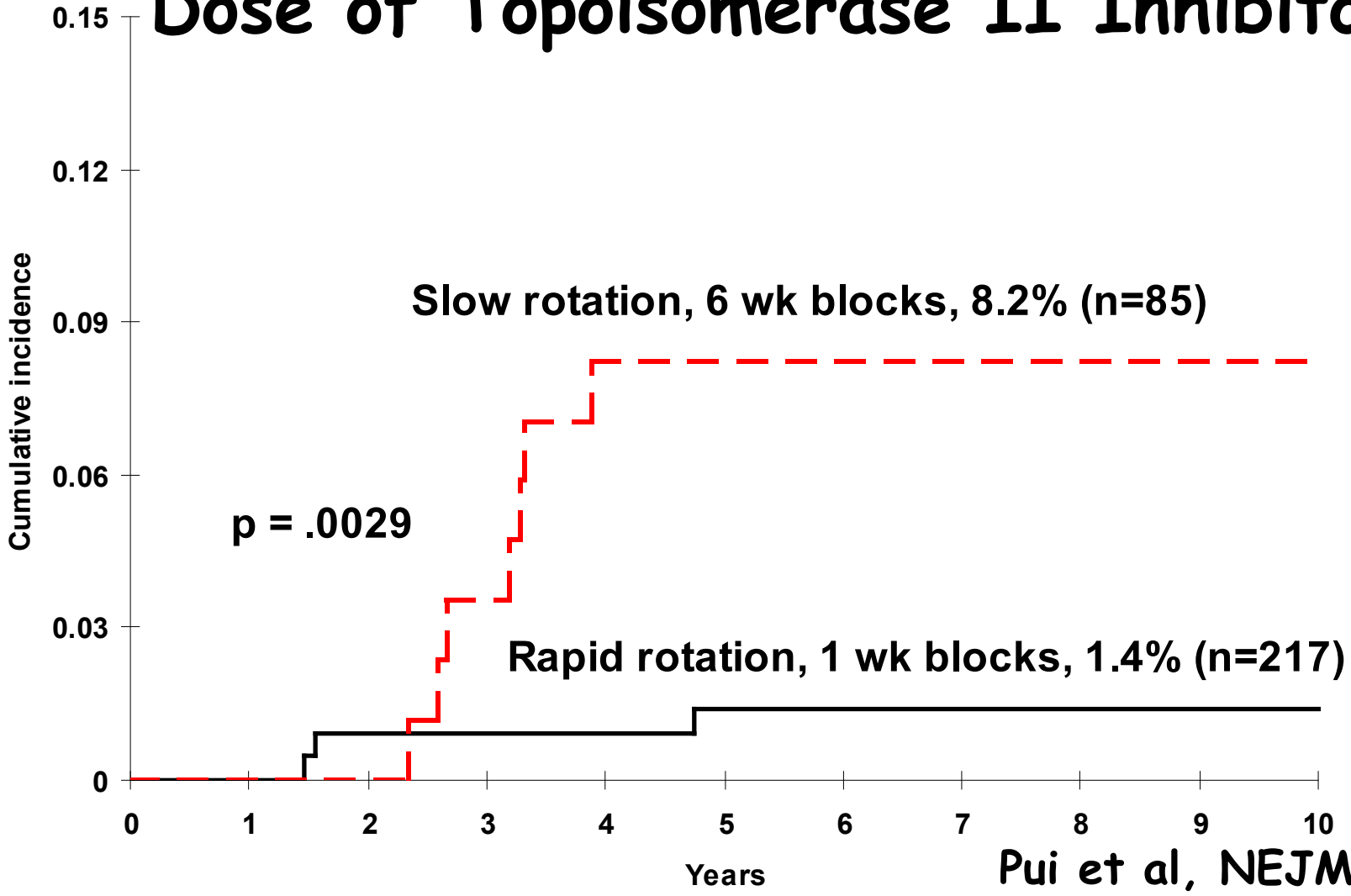
SJCRH Total XI: Two Tx Arms

Week	II	III
1	VP + cyclo	VP + cyclo
2	MP + MTX	VP + cyclo
3	VM + AraC	VP + cyclo
4	Pred + VCR	VP + cyclo
5	VP + cyclo	VP + cyclo
6	MP + MTX	VP + cyclo
7	VM + AraC	MP + MTX
8	Pred + VCR	MP + MTX
9	VP + cyclo	MP + MTX
10	MP + MTX	MP + MTX
11	VM + AraC	MP + MTX
12	Pred + VCR	MP + MTX
13	VP + cyclo	VM + AraC
14	MP + MTX	VM + AraC
15	VM + AraC	VM + AraC
16	Pred + VCR	VM + AraC
to wk 120		
Cum.Dose:	18 g	18 g

Cumulative doses of all drugs identical

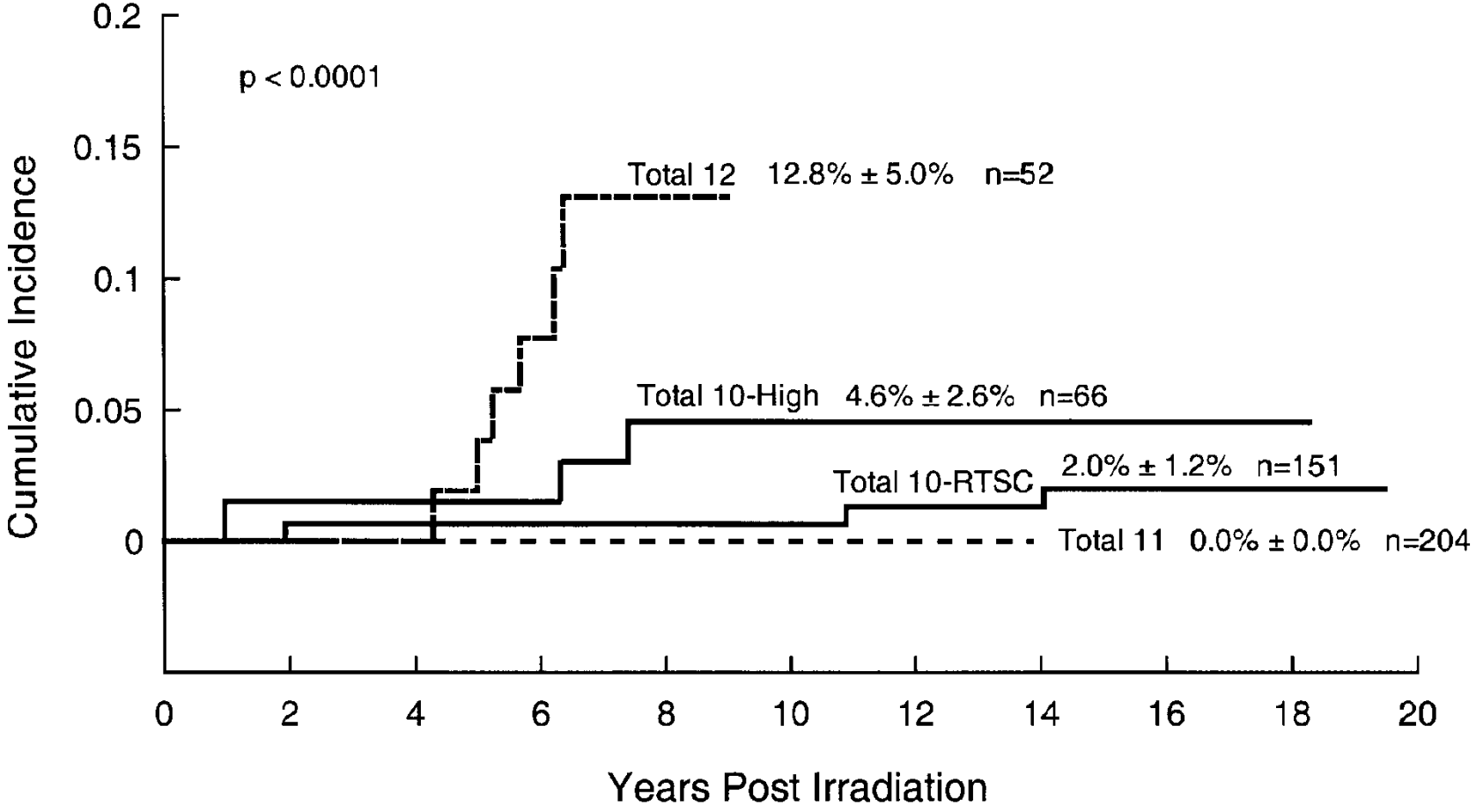
Pui et al, NEJM, 1991

Risk of t-AML differed by tx arms; unrelated to Cumulative Dose of Topoisomerase II Inhibitors



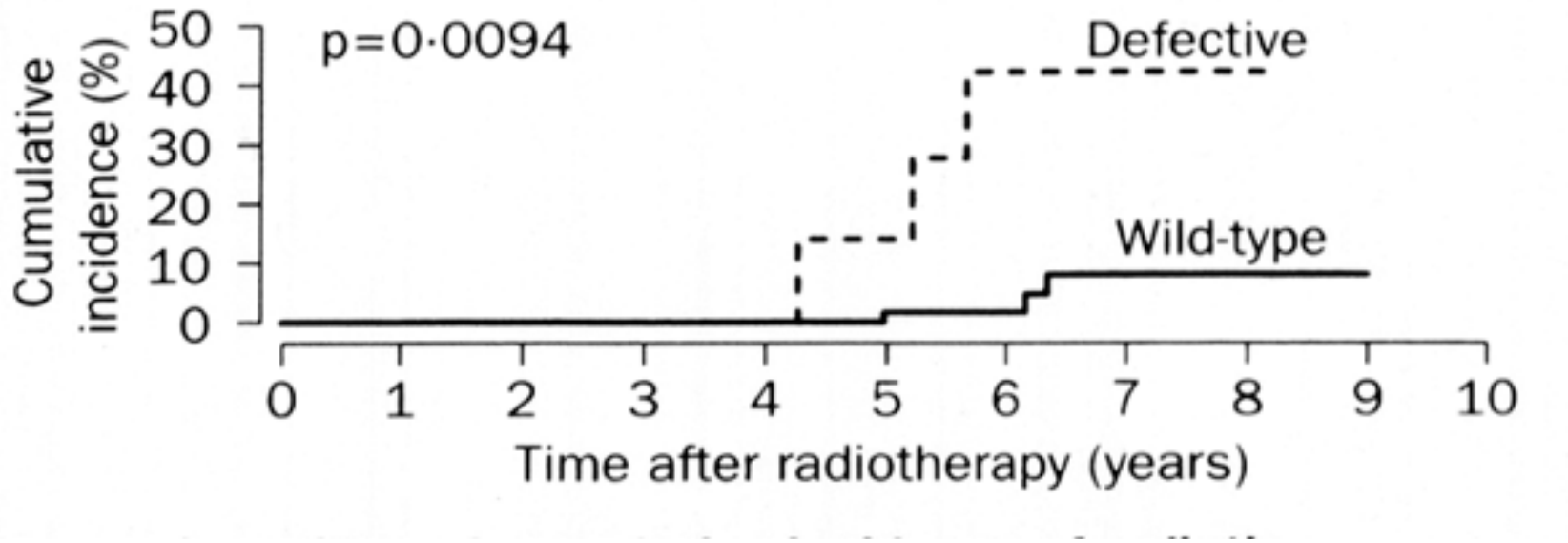
Pui et al, NEJM, 1991

An unusually high incidence of secondary brain tumors for Total XII Study; all protocols had identical doses of cranial irradiation



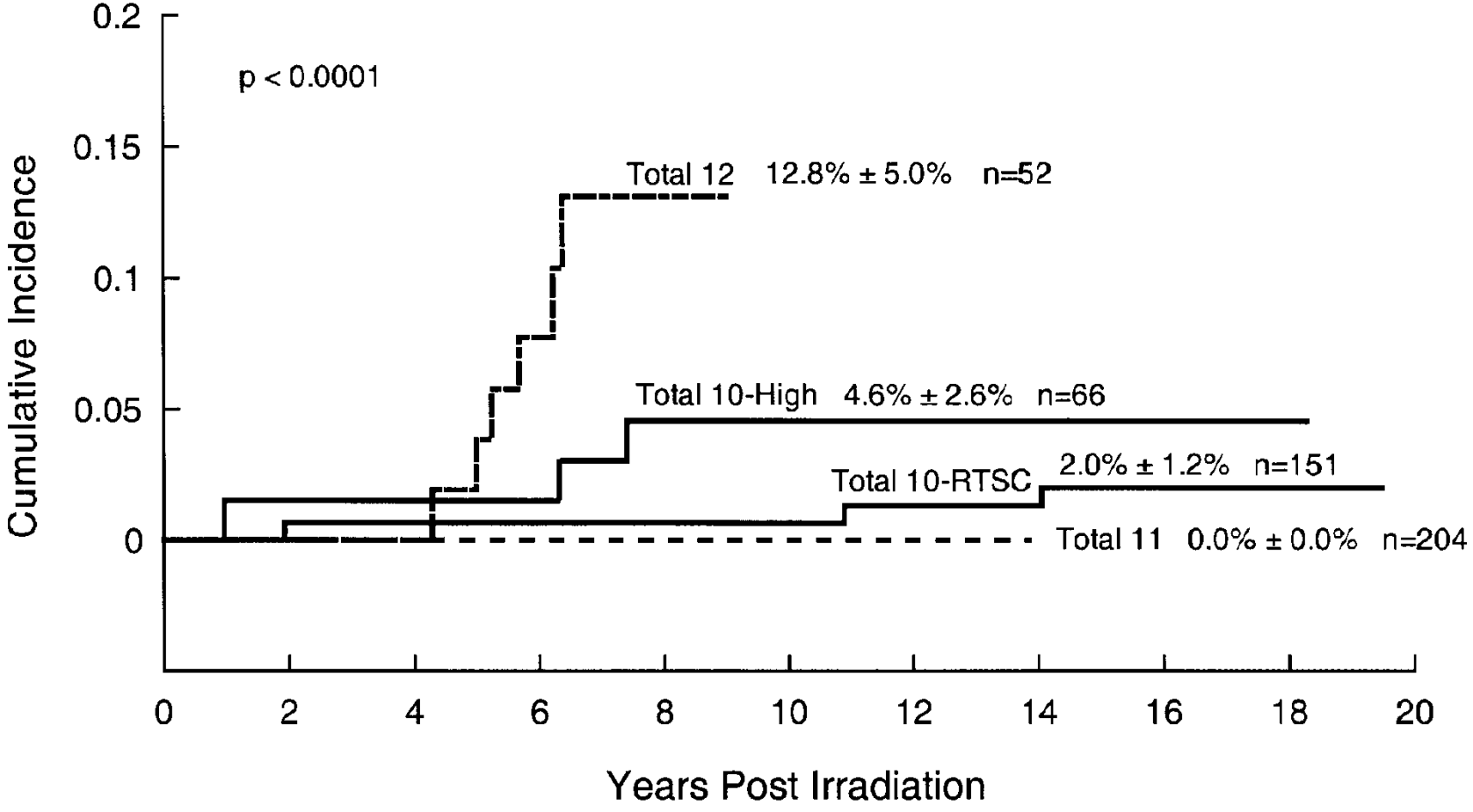
Relling et al *Lancet* 1999 354:34-39

Within Total XII protocol, TPMT defects associated with brain tumor



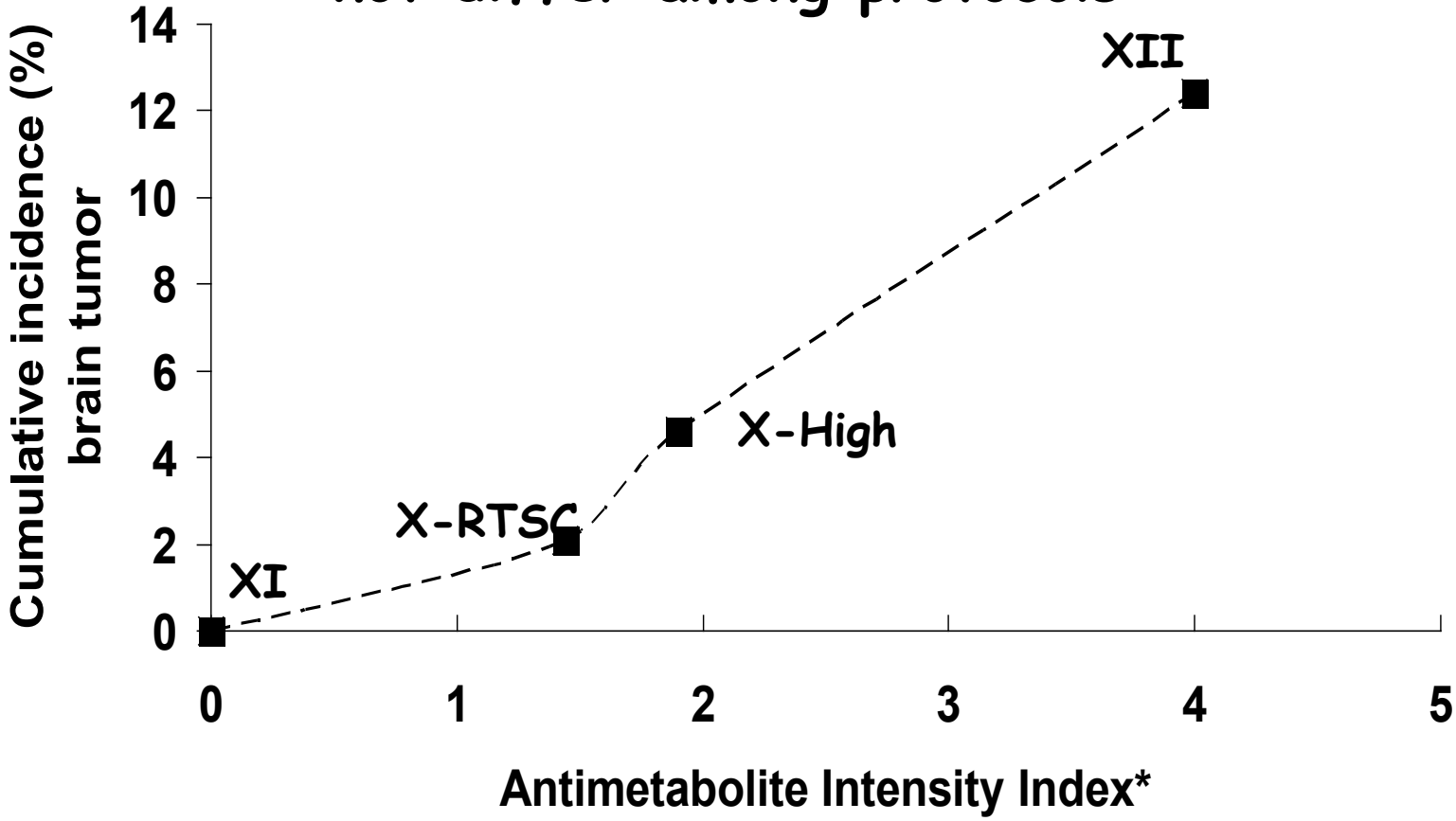
Relling et al *Lancet* 1999 354:34-39

Pts with TPMT Defects have always been around—so what was different about Total 12?



Relling et al *Lancet* 1999

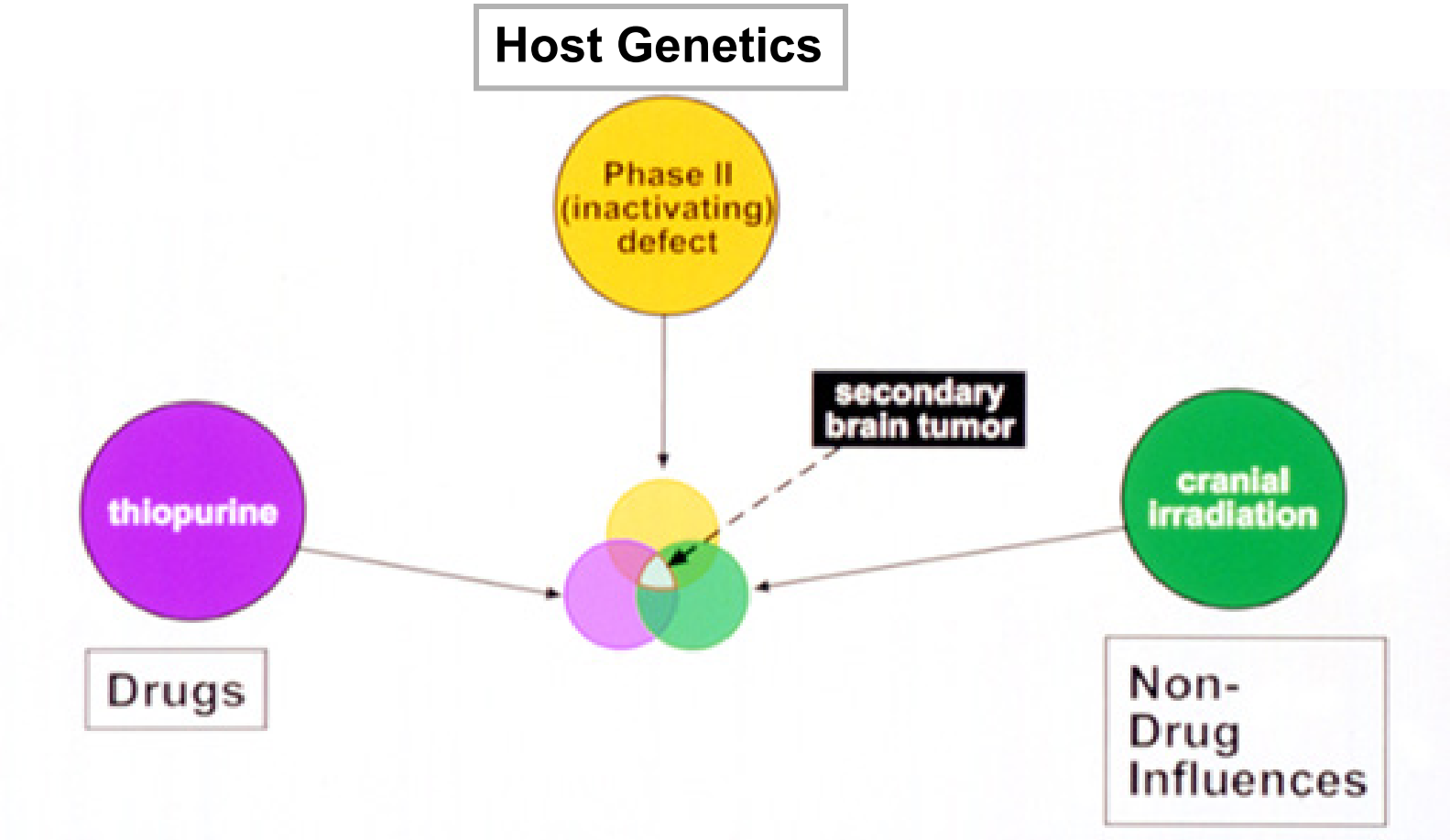
The intensity of antimetabolite Intensity (during irradiation) correlated with Risk of Brain Tumor---although cumulative doses of antimetabolites did not differ among protocols



* Score = 1 for ITs during rads, -1 for LV during rads, 2 for systemic MTX during rads, 2 for full dose 6MP during rads

Lancet 1999

Phenotypic consequence of genetic Defect depends on detailed interactions of Drug and radiation therapy



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Points

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- If you are ready to implement, implement
  - Pharmacogenetics: 13 genes, ~ 60 drugs max

- If you are not convinced it works:
  - Randomize---but then isn't that clinical research, not implementation?
  - Capitalize on our non-uniform health care "system" to randomize for you
  - Historic controls: risk poor study design and misleading answers