Therapy-Related Leukaemia

What is it? Who has it? Are you sure?

Robert Peter Gale MD, PhD, DSc (hon), FACP, FRSM

Imperial College London

UCLA Medical Center

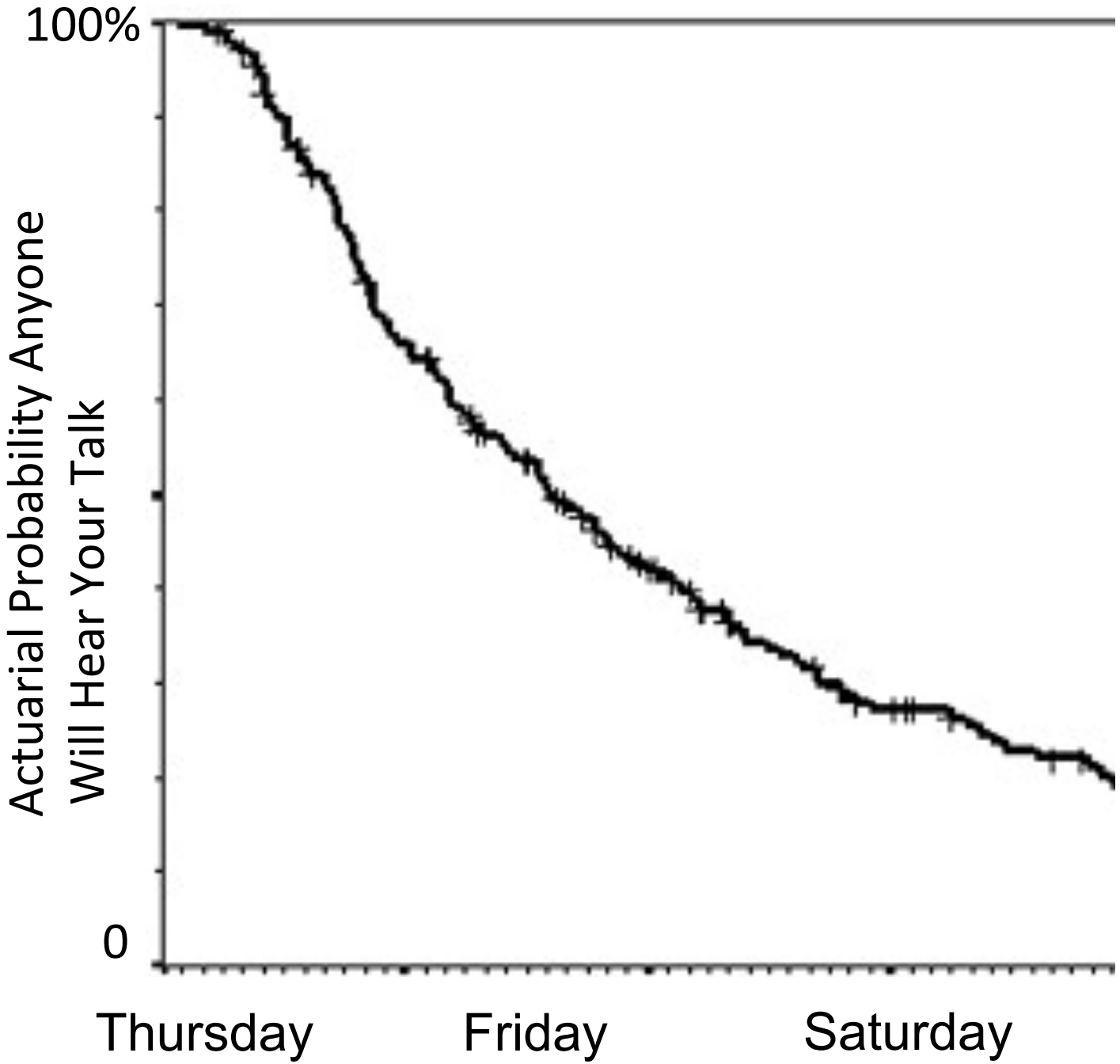
Celgene Corp

Disclosure

Celgene Corp

Fusion Pharma

StemRad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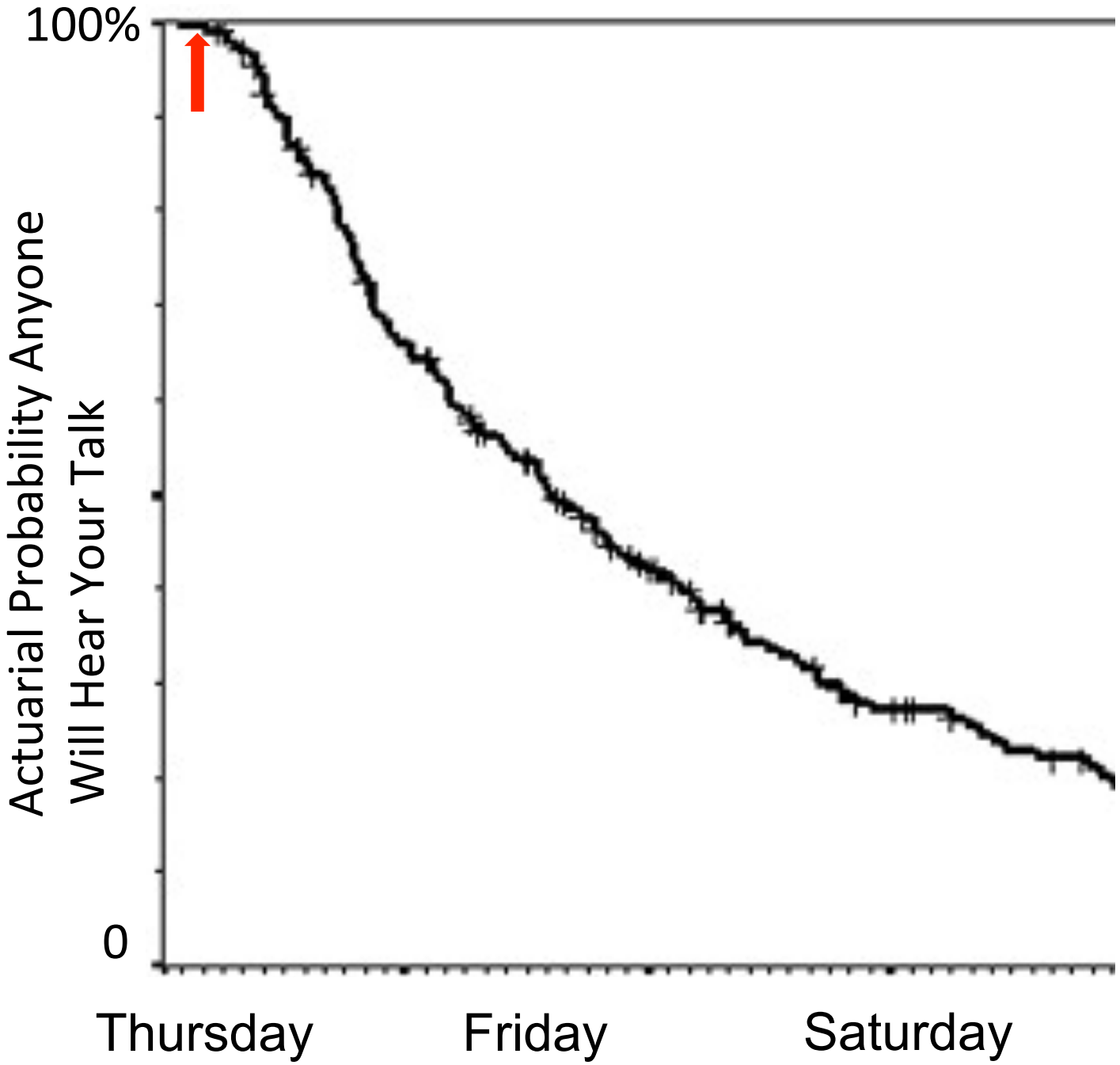
Actuarial Probability Anyone
Will Hear Your Talk
Thursday
Friday
Saturday


100%
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Actuarial Probability Anyone
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FIFTH
INTERNATIONAL SYMPOSIUM ON SECONDARY LEUKEMIA AND LEUKEMOGENESIS

HONORARY PRESIDENT: GIUSEPPE LEONE

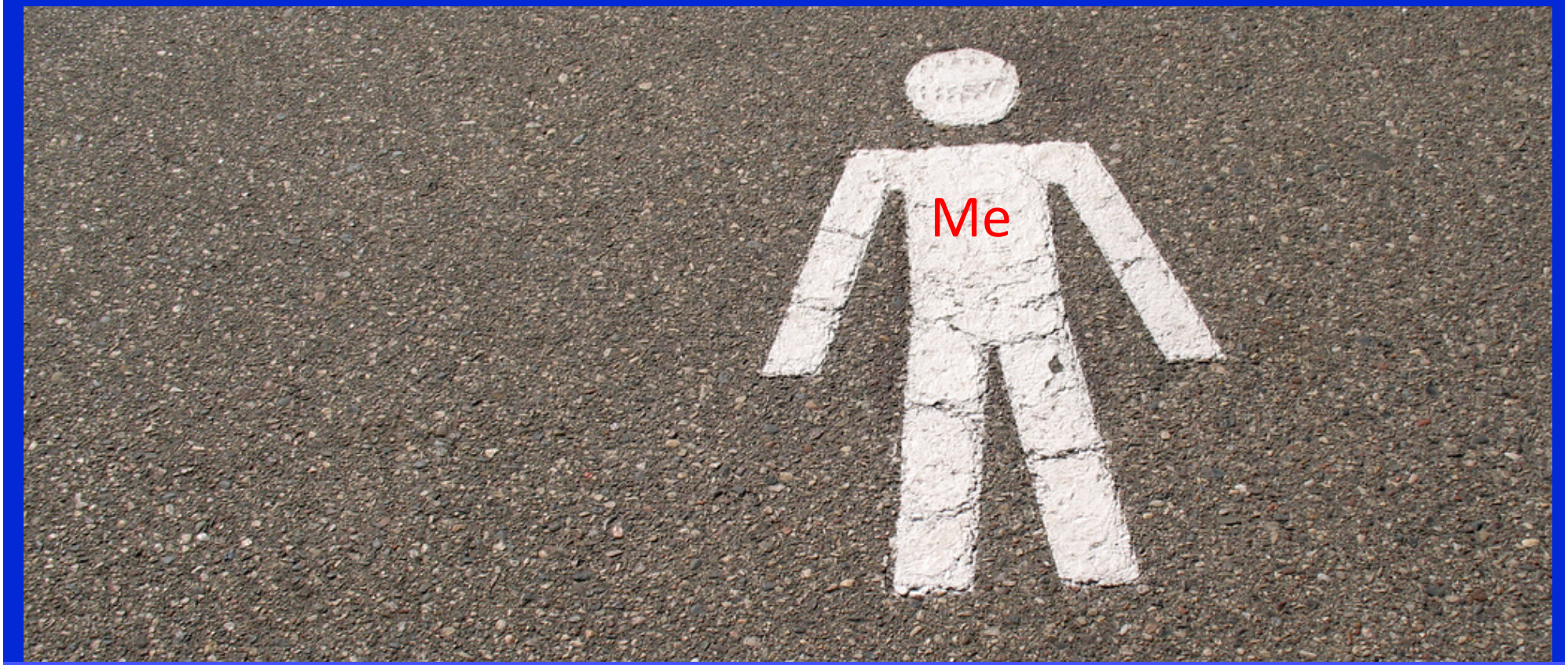
CONGRESS ORGANIZERS: FRANCESCO LO COCO, LIVIO PAGANO, MARIA TERESA VOSO

ROMA, SEPTEMBER 22-24, 2016

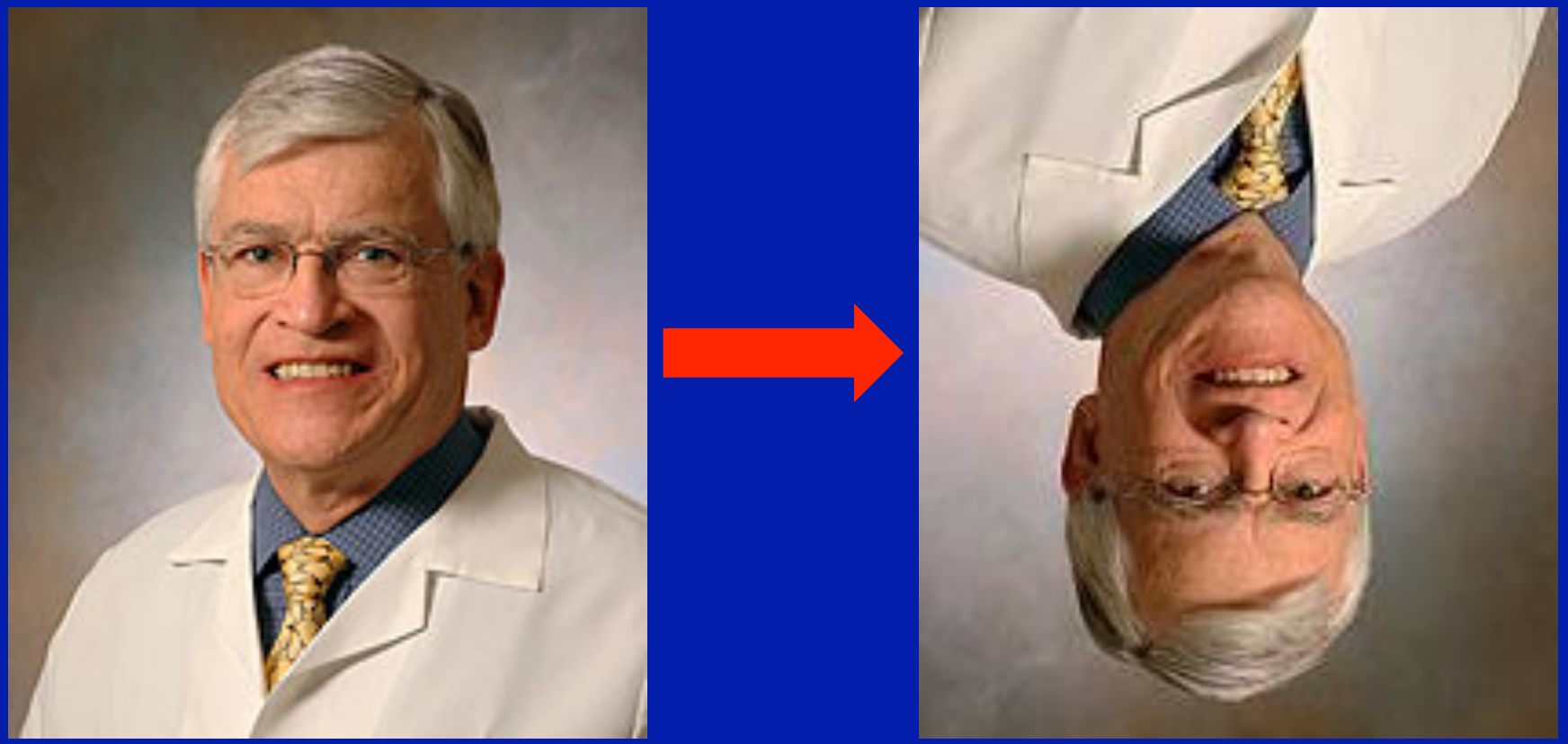
Secondary leukaemia OR *second* cancer?

2° AML
2° AML
2° AML
2° AML
Me

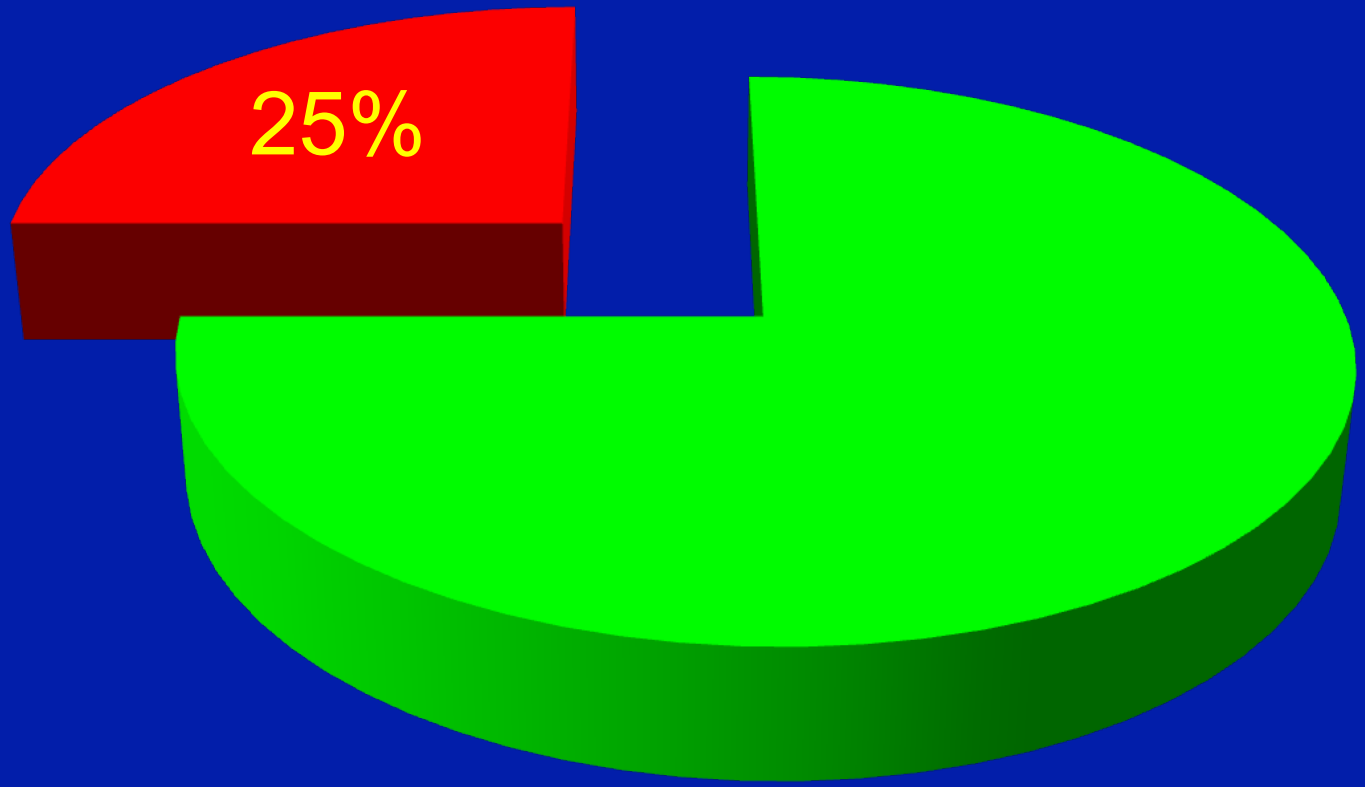
Likely Outcome



Apoplexy



Secondary or *Therapy-Related* Leukaemia



If a man will begin with certainties, he shall end in doubts, but if he will be content to begin with doubts, he ~~shall~~ may end in certainties.

Francis Bacon

Questions

What is *secondary* or *therapy-related* leukaemia?

Who has it?

Can we diagnose it accurately?

My 3 problems…

Apophenia

Conjunction fallacy

Evolutionary drive to think you are right

My 3 problems…

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Apophenia

The human tendency to perceive meaningful patterns within random data

My 3 problems…

Apophenia

Conjunction fallacy

Evolutionary drive to think you are right

Are you intelligent OR rational?

65 year old man with newly-diagnosed AML worked in a nuclear power facility for 30 years. His weekend hobby is making model airplanes using petroleum-based glues in a closed workspace. A survey of his basement shows high radon level. The mostly likely cause of his AML is…

Radiation

Radiation and benzene

Radiation, benzene and radon

Radiation

Radiation and benzene

Radiation, benzene and radon

Radiation

Radiation and benzene

Radiation, benzene and radon

Radiation

Radiation and benzene

Radiation, benzene and radon

Correct

Radiation

Radiation and benzene

Radiation, benzene and radon

My 3 problems…

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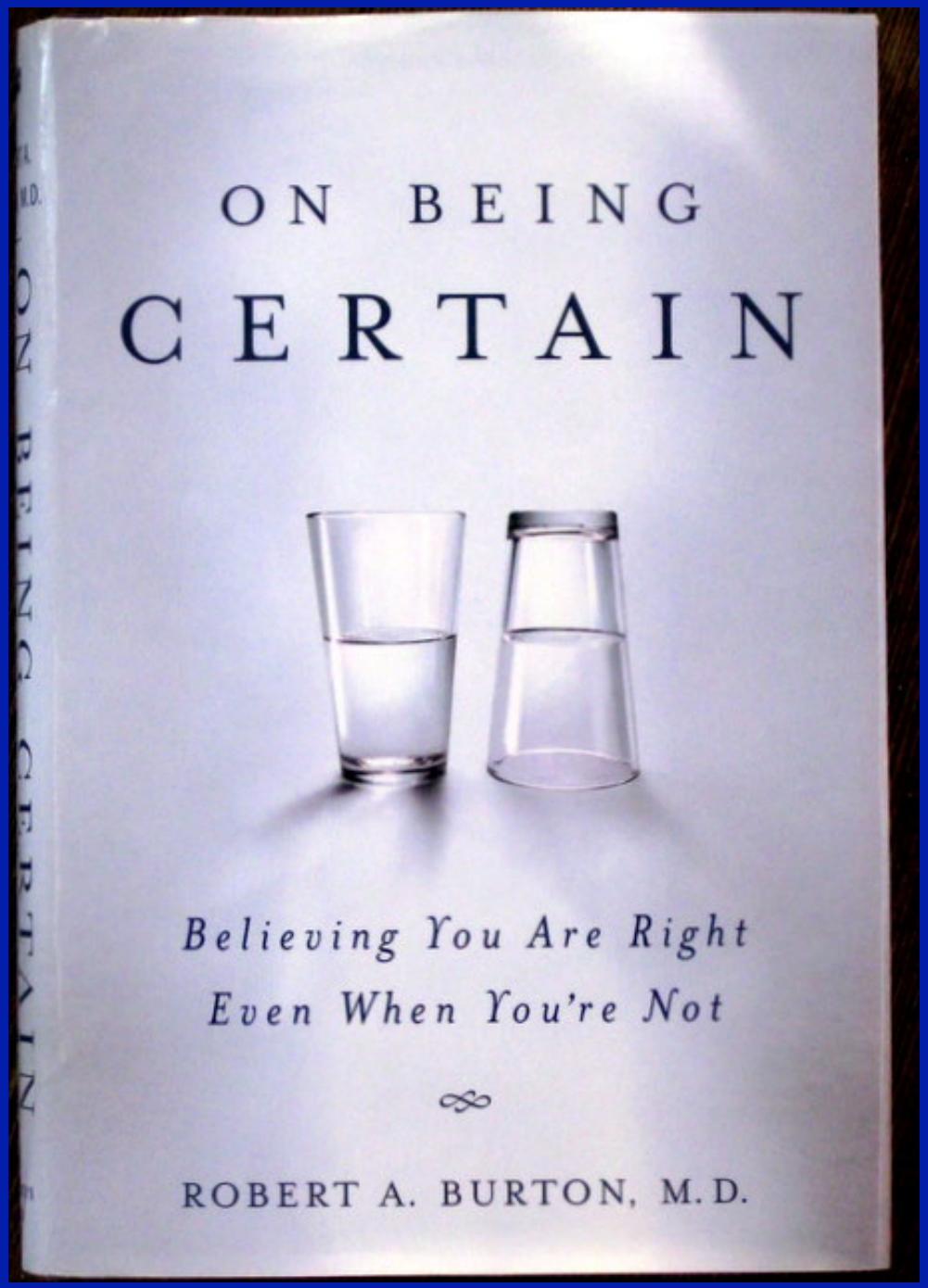
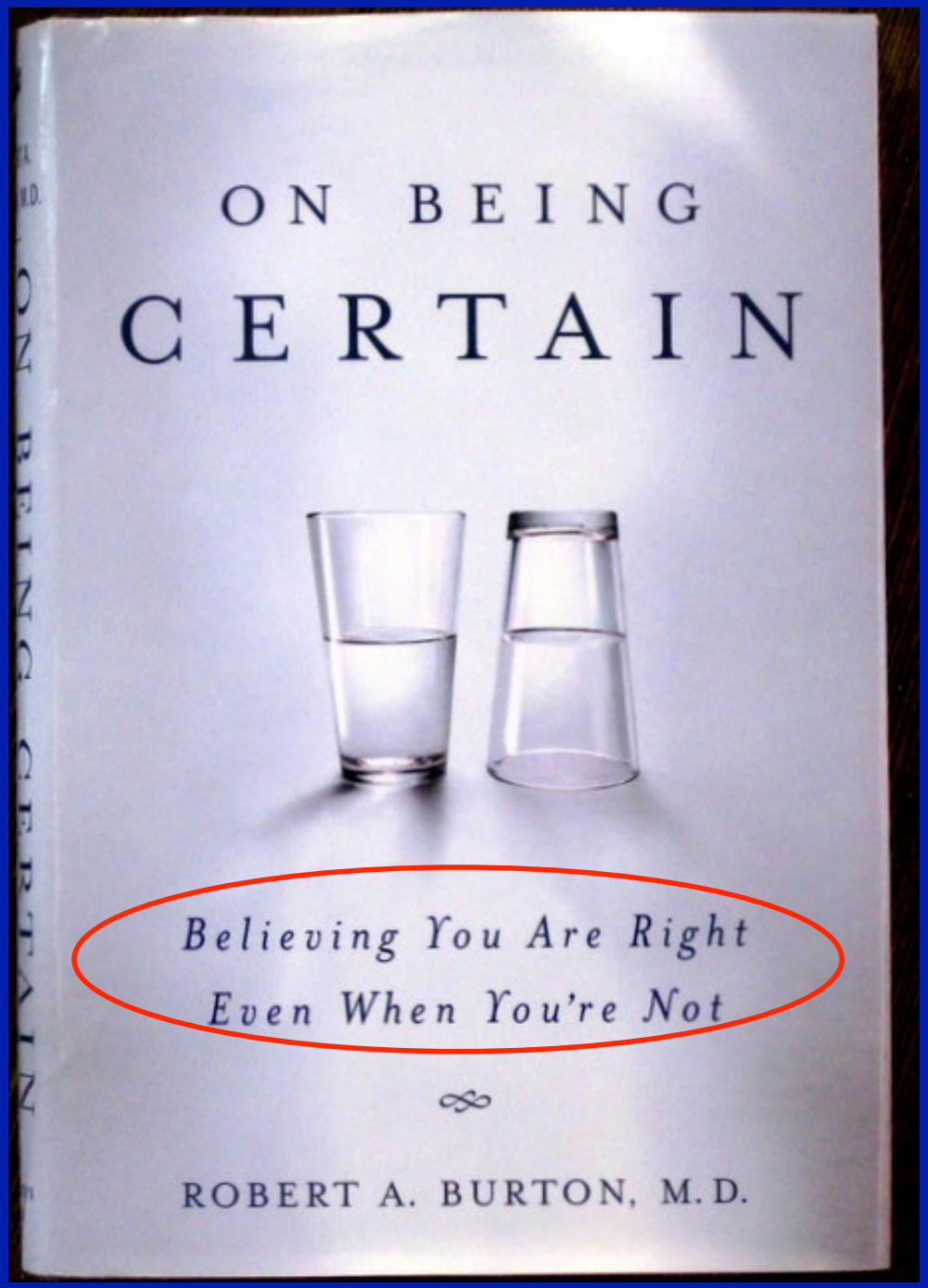

ON BEING
CERTAIN
Believing You Are Right
Even When You're Not
ROBERT A. BURTON, M.D.
ON BEING CERTAIN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Secondary or *Therapy-Related* Leukaemia

A leukaemia *known to be* caused by or contributed to by exposure to DNA-damaging (mutagenic) agents such as ionizing radiations, drugs or chemicals

Typical Variables

Older age

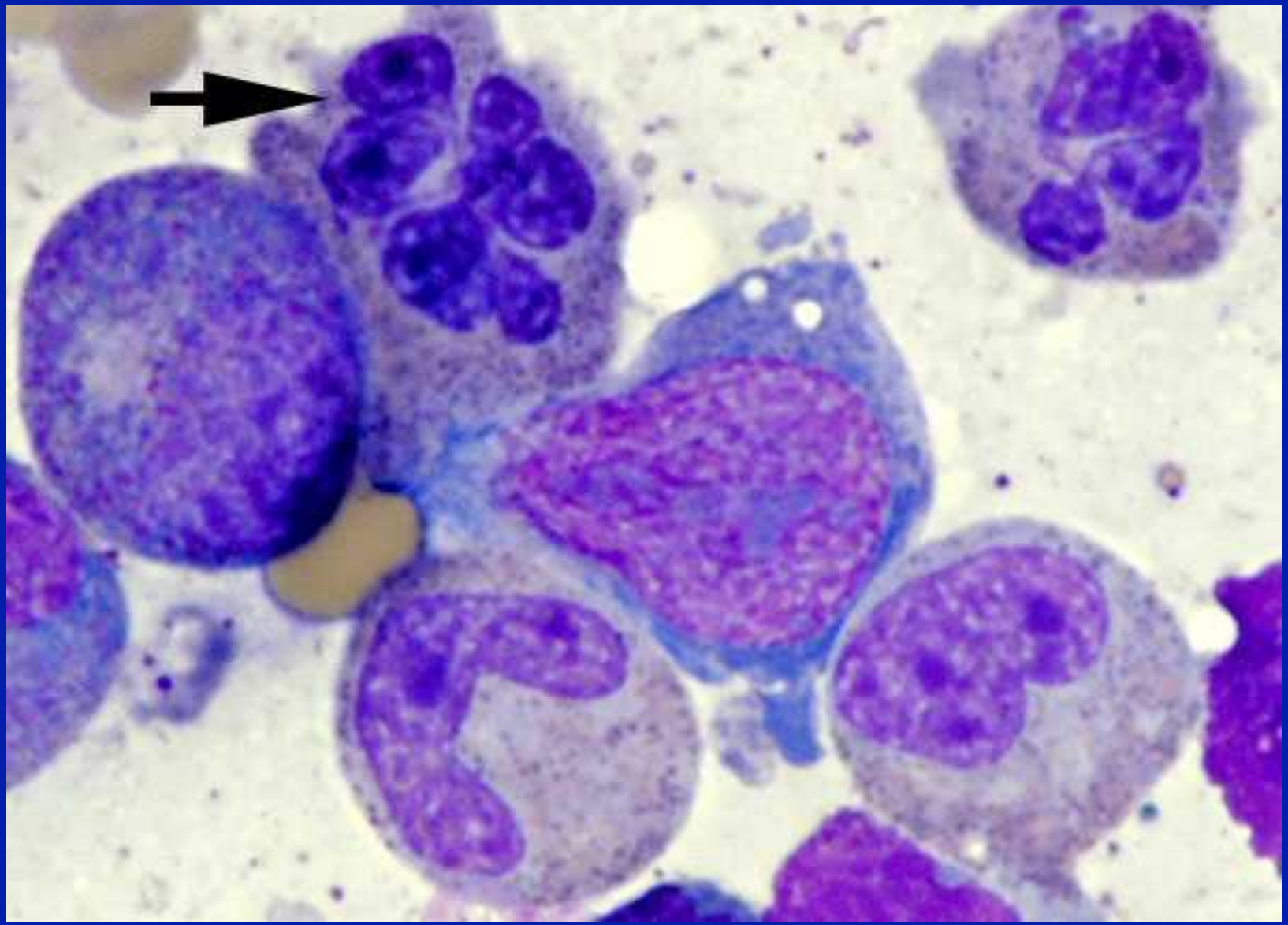
Antecedent haematologic disorder/MDS

Anaemia, Decreased WBC, platelets

Dysplastic bone marrow

Cytogenetic abnormalities del(5/5q), del(7/-7q), del (3p), del(17p), t(18;21), t(3;21), t(8;21), t(x;11q23)

Mutations *EVI1, AML1/2, MLL, NRAS, FANC, XPD, NQ01*



But….

None of these features is unique to *secondary* or *therapy-related* leukaemia

Some Exposures Implicated in Therapy-Related Leukaemia

Ionizing radiations

DNA-alkylating drugs

Topoisomerase-2-inhibitors

Benzene

Radon

Smoking

Formaldehyde

Anti-Cancer Drugs Linked to Leukaemia

Alkeran
Busulfan
Cyclophosphamide
Chlorambucil
Cisplatin
Doxorubicin
Etoposide
Melphalan
Mitoxantrone
Nitrogen mustard
Nitrosoureas
Thiotepa

Caveats

Not all anti-cancer drugs cause *therapy-related* leukaemia

Not all exposures to relevant drugs cause *therapy-related* leukaemia

If you see someone with leukaemia exposed to one of these *agents does they have* therapy-related leukaemia?

Problems with these analyses

They reflect associations, not *cause-and-effect*

The calculations assume you know who has *secondary* or *therapy-related* leukaemia

Associations refer to cohorts not individuals

Questions

What is *secondary* or *therapy-related* leukaemia?

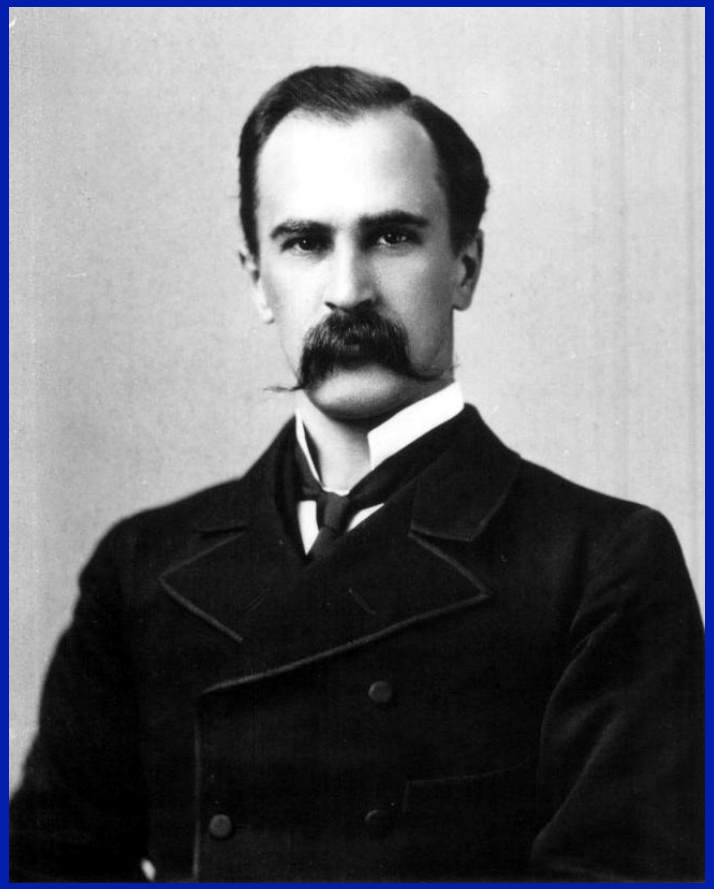
Who has it?

Can we diagnose it accurately?

Why are statistics important?

To understand God's thoughts we must study statistics for these are the measure of his purpose

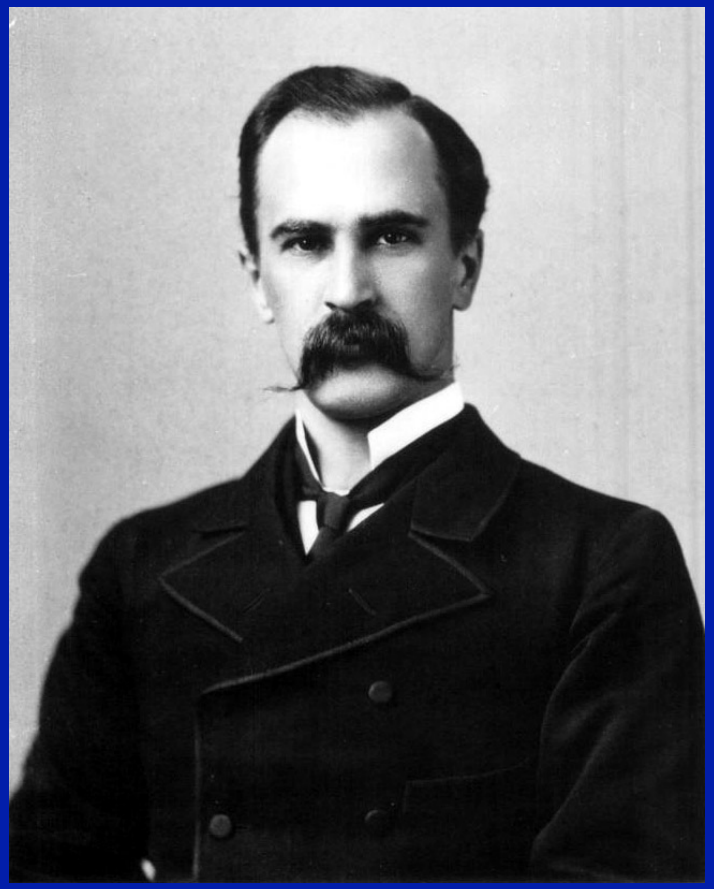
Florence Nightingale



The science of medicine is uncertainty.

The art of medicine is probability.

Sir William Osler.



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Sir William Osler.

How do epidemiologists view causation?

Probability of Causation

$$\text{Probability of Causation (Assigned Share)} = \frac{\text{Excess Relative Risk}}{\text{Relative Risk}} \times 100\%$$

Variables Needed to Calculate Probability of Causation

Agent

Dose

Schedule

Age at exposure

Gender

Interval from exposure to leukaemia

Potential confounders (prior cancer, genetic disorder, smoking *etc.)*

Variables Needed to Calculate PC

Agent

Dose

Schedule

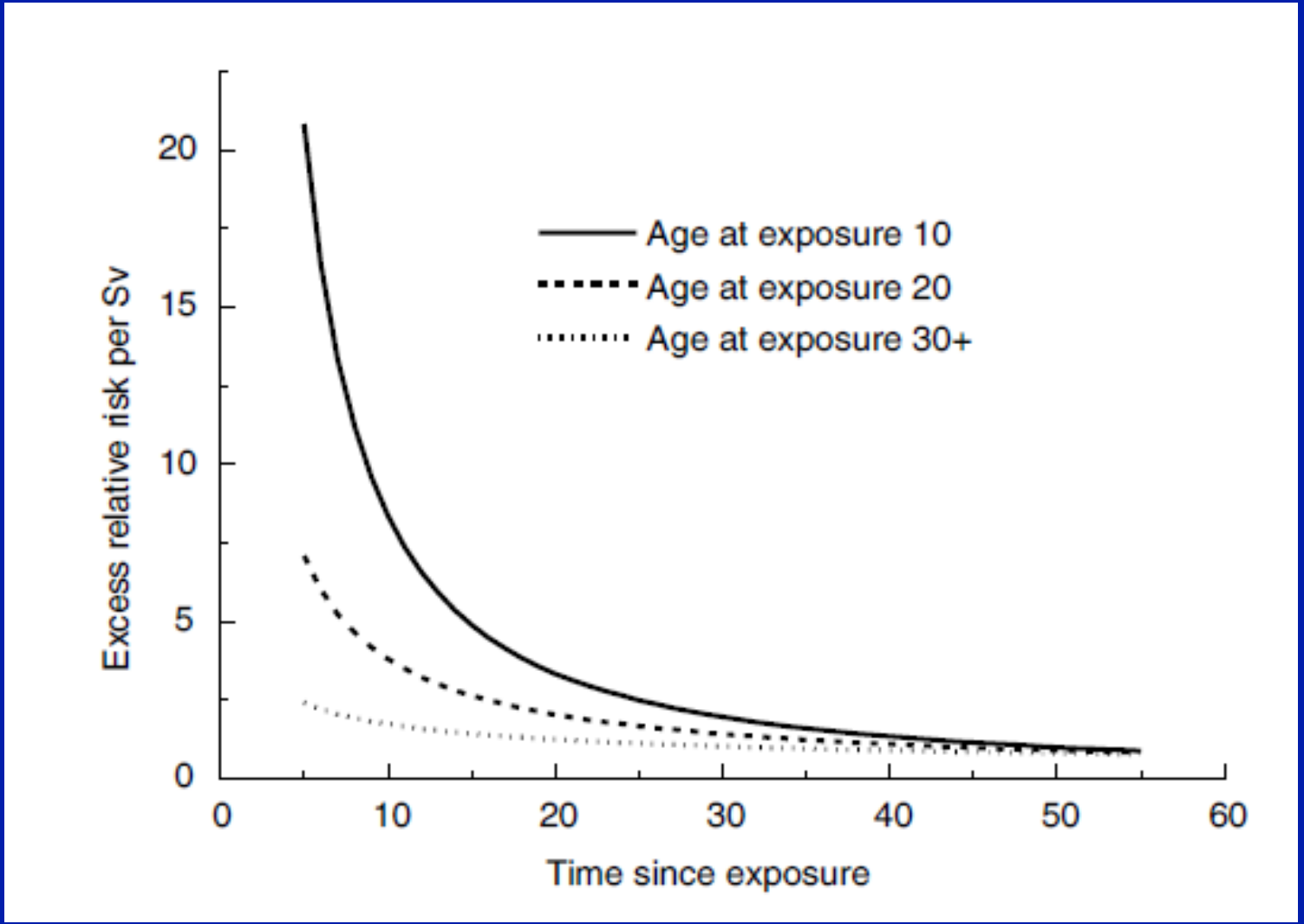
Age at exposure

Gender

Interval from exposure to leukaemia

Potential confounders (prior cancer, genetic disorder, smoking *etc.)*

A-Bombs and Leukaemia



Variables Needed to Calculate PC

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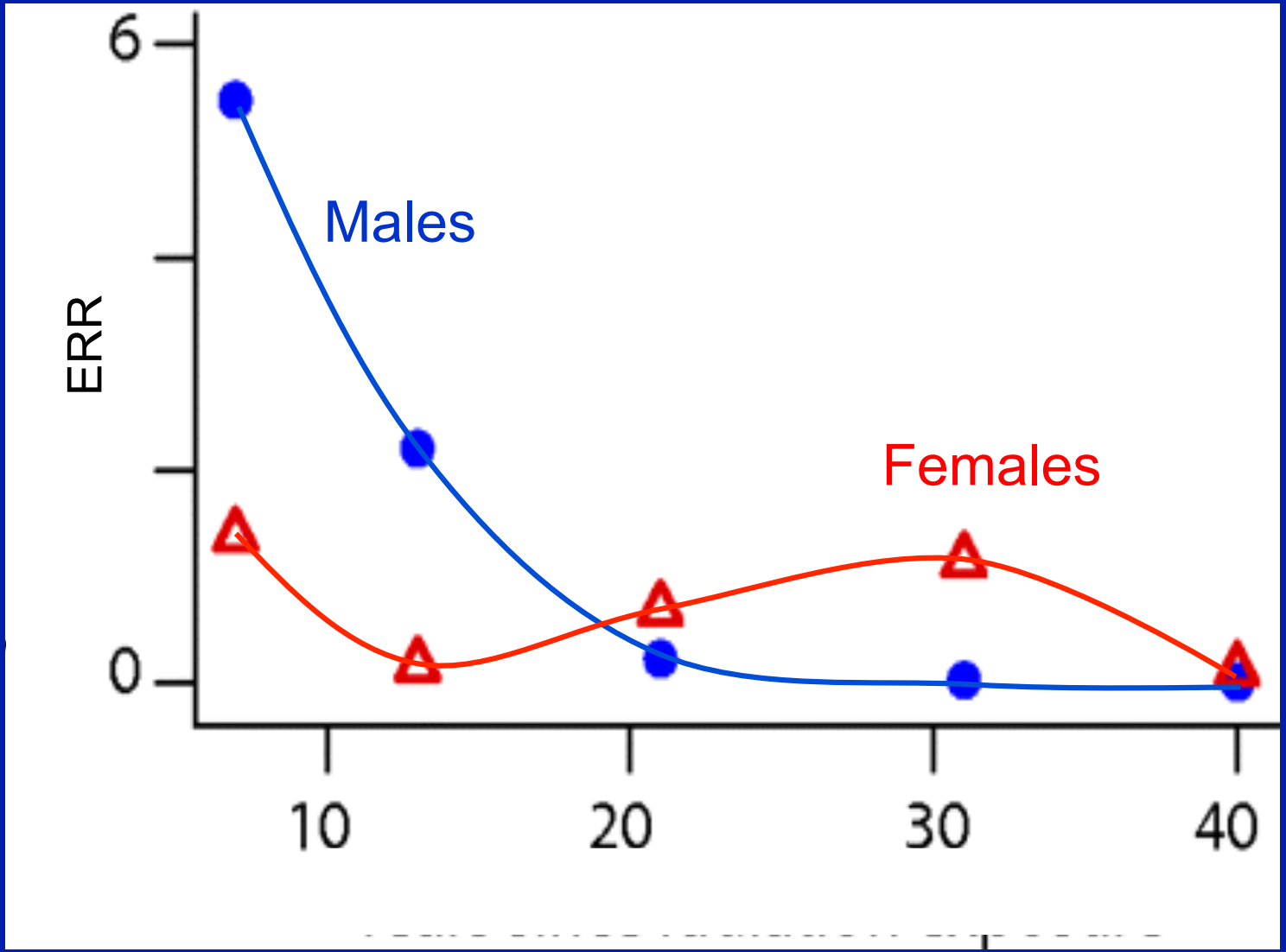
CML after A-Bombs



Probability of Causation

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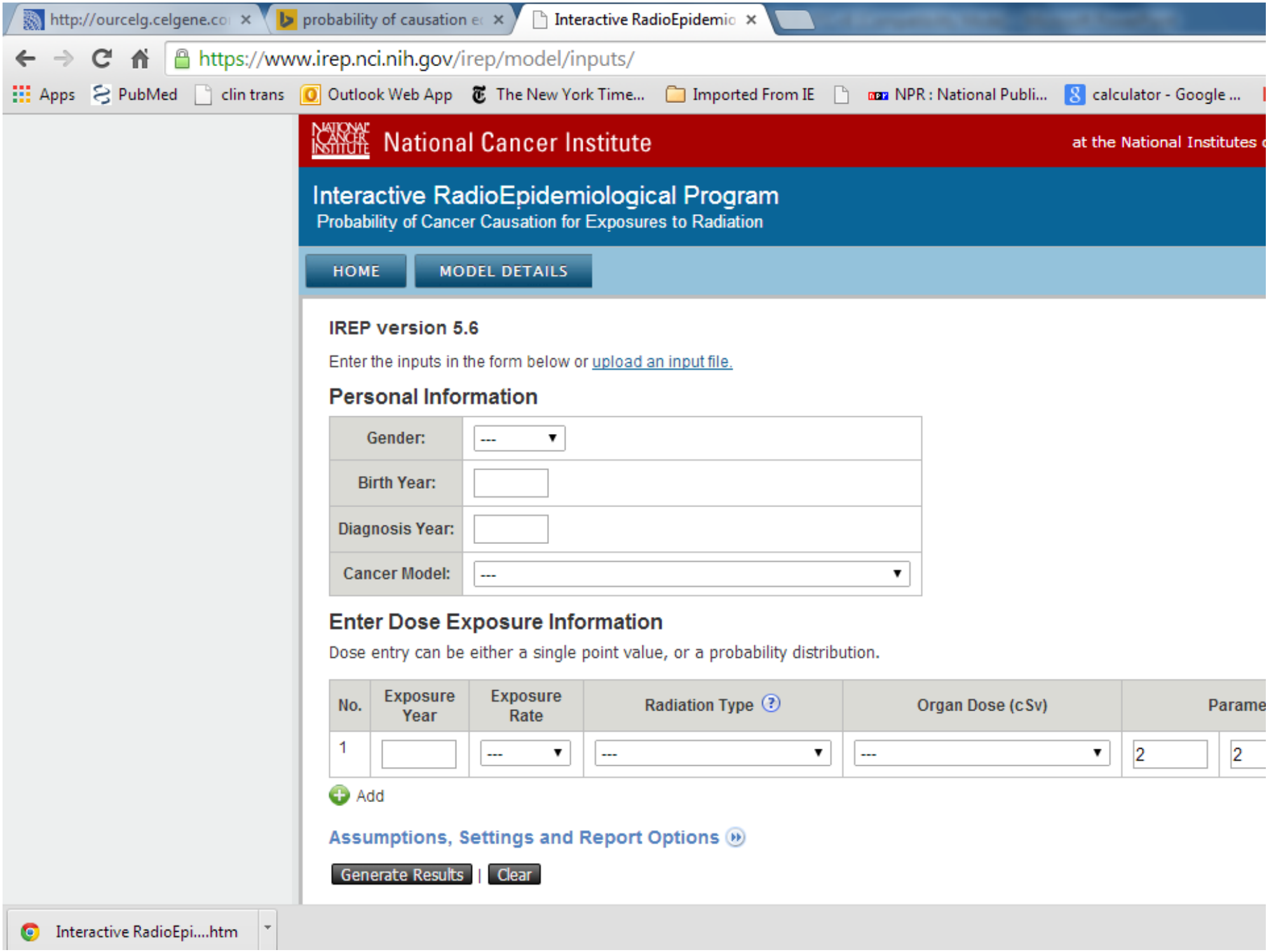
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probability of causation e
Interactive RadioEpidemio
https://www.irep.nci.nih.gov/irep/model/inputs/
Apps
PubMed
clin trans
Outlook Web App
The New York Time...
Imported From IE
NPR : National Publi...
calculator - Google ...
National Cancer Institute
at the National Institutes
Interactive RadioEpidemiological Program
Probability of Cancer Causation for Exposures to Radiation
HOME
MODEL DETAILS
IREP version 5.6
Enter the inputs in the form below or upload an input file.
Personal Information
Gender:

Birth Year:
Diagnosis Year:
Cancer Model:

Enter Dose Exposure Information
Dose entry can be either a single point value, or a probability distribution.
No.
Exposure Year
Exposure Rate
Radiation Type
Organ Dose (cSv)
Parame
1

2
2
Add
Assumptions, Settings and Report Options
Generate Results
Clear
Interactive RadioEpi....htm

Probability of Causation

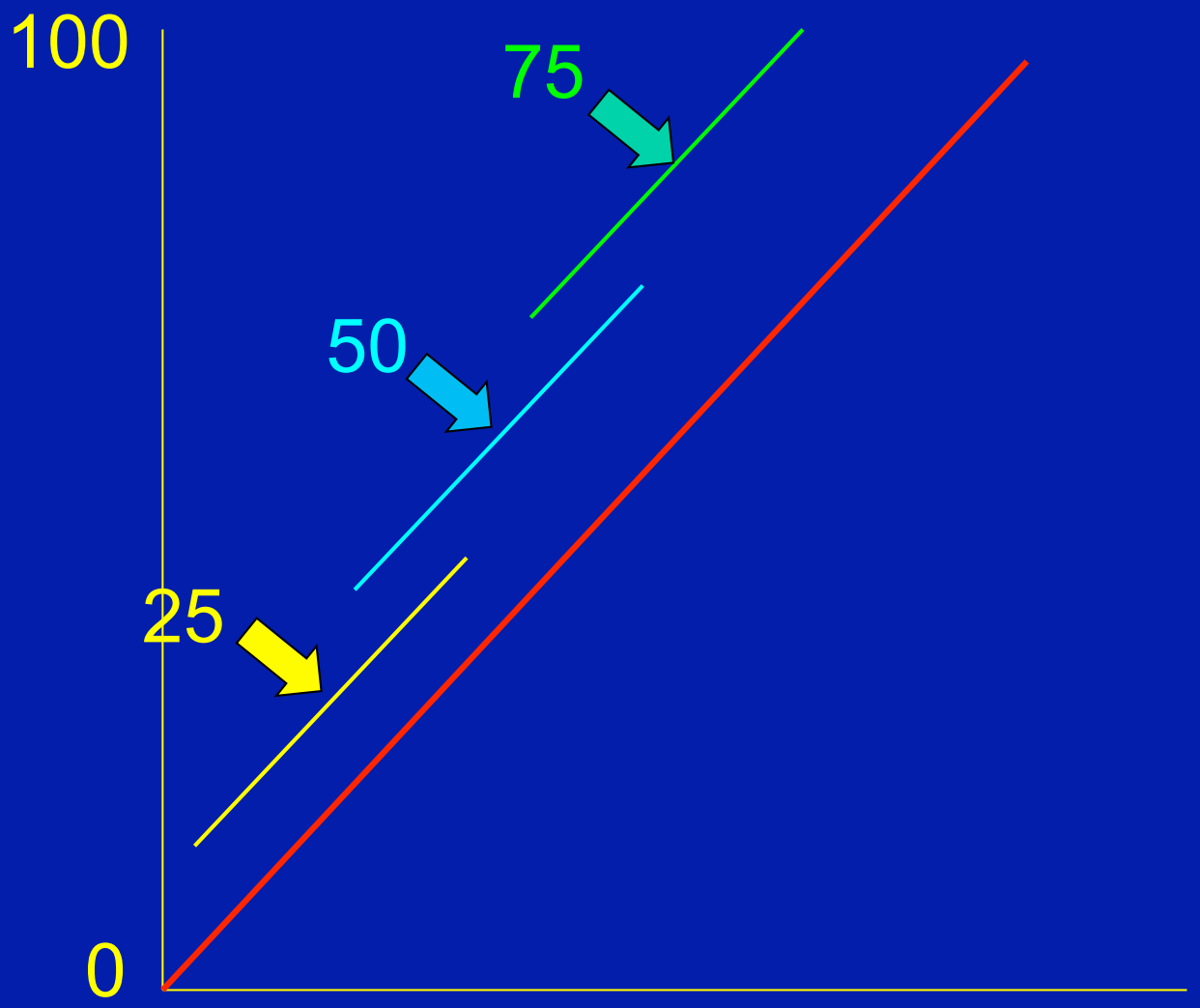
45% (95% CI, 25, 65%)

Limitations

In clinical setting we rarely have data needed to calculate a PC

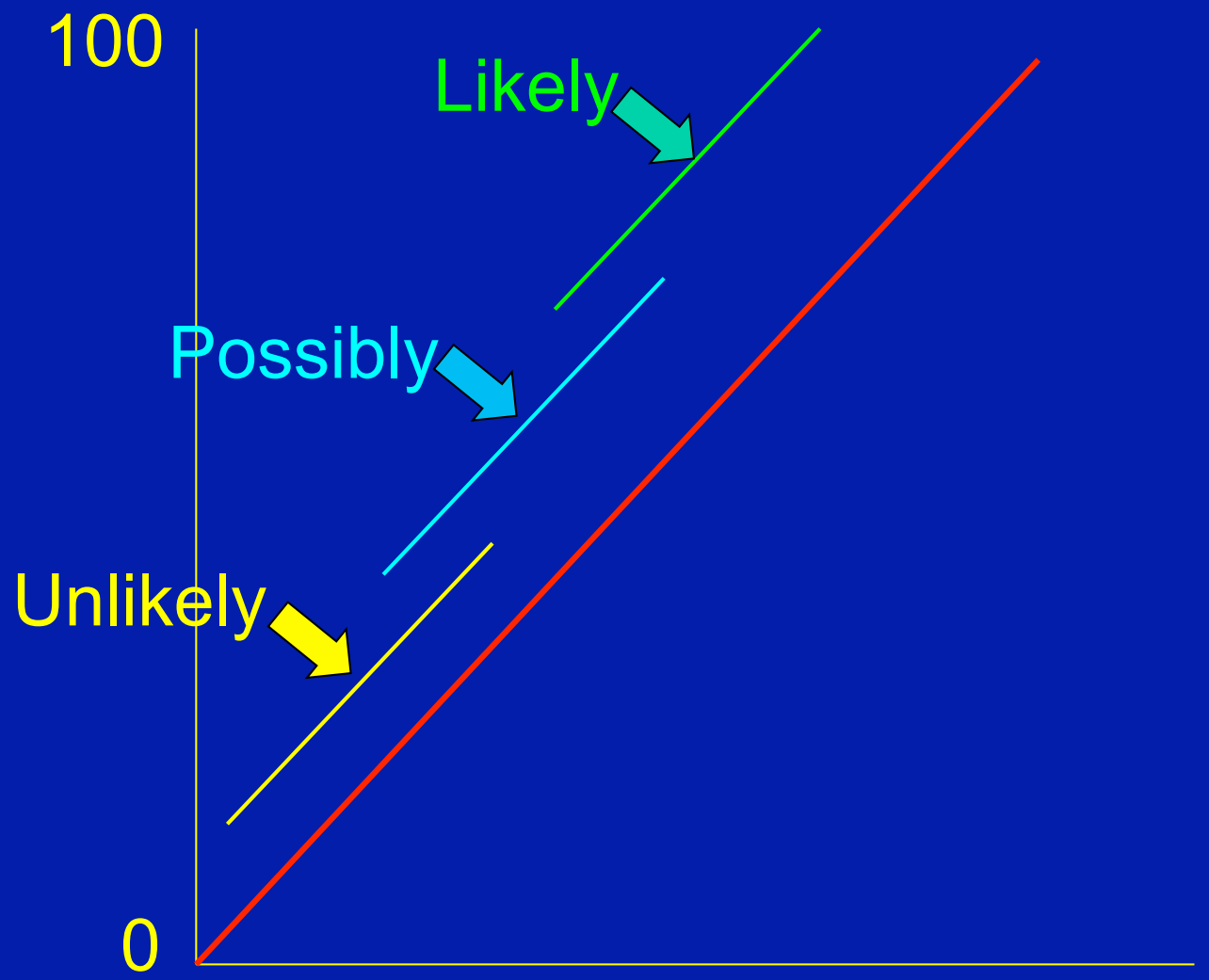
We lack statistical programs to calculate PC for exposures other than radiation

PC Calculation



Consequently, it is best to use estimates such as *likely, possible, unlikely* which encompass uncertainty rather than a binary (Y/N) with no expression of uncertainty

PC Calculation



Why is any of this important?

Why is uncertainty important

Mis-labeling someone as having *therapy-related leukaemia* can result in a fatal physician error

No therapy because the situation is hopeless or a transplant because nothing else will work

Questions

What is *secondary* or *therapy-related* leukaemia?

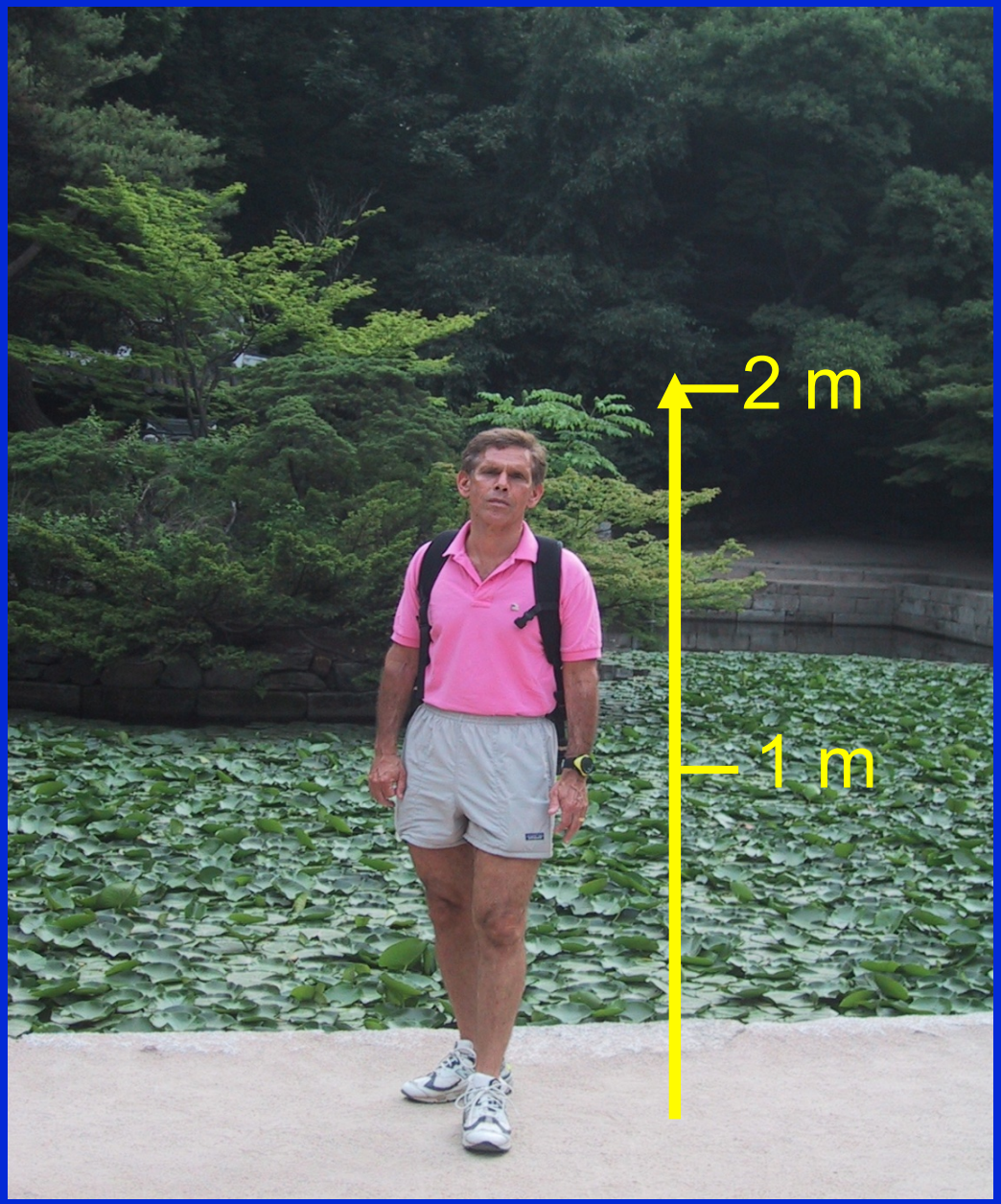
Who has it?

Can we diagnose it accurately?

What is the difference between an estimate and a guess?

How tall is Bob Gale?

Estimate



Is Bob Gale’s wife beautiful?

Guess

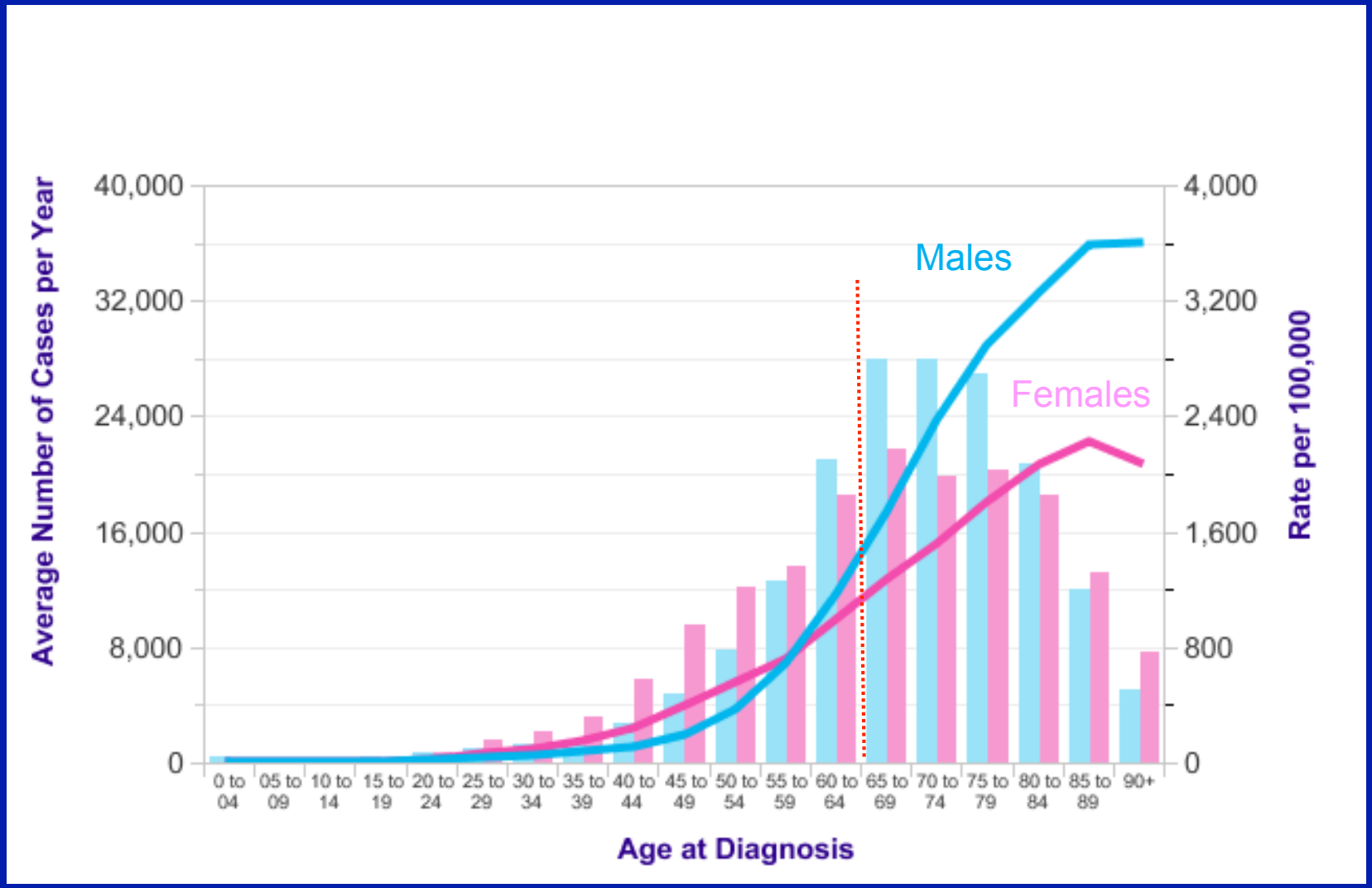
Compared to what?

How can I know, I've never seen her?

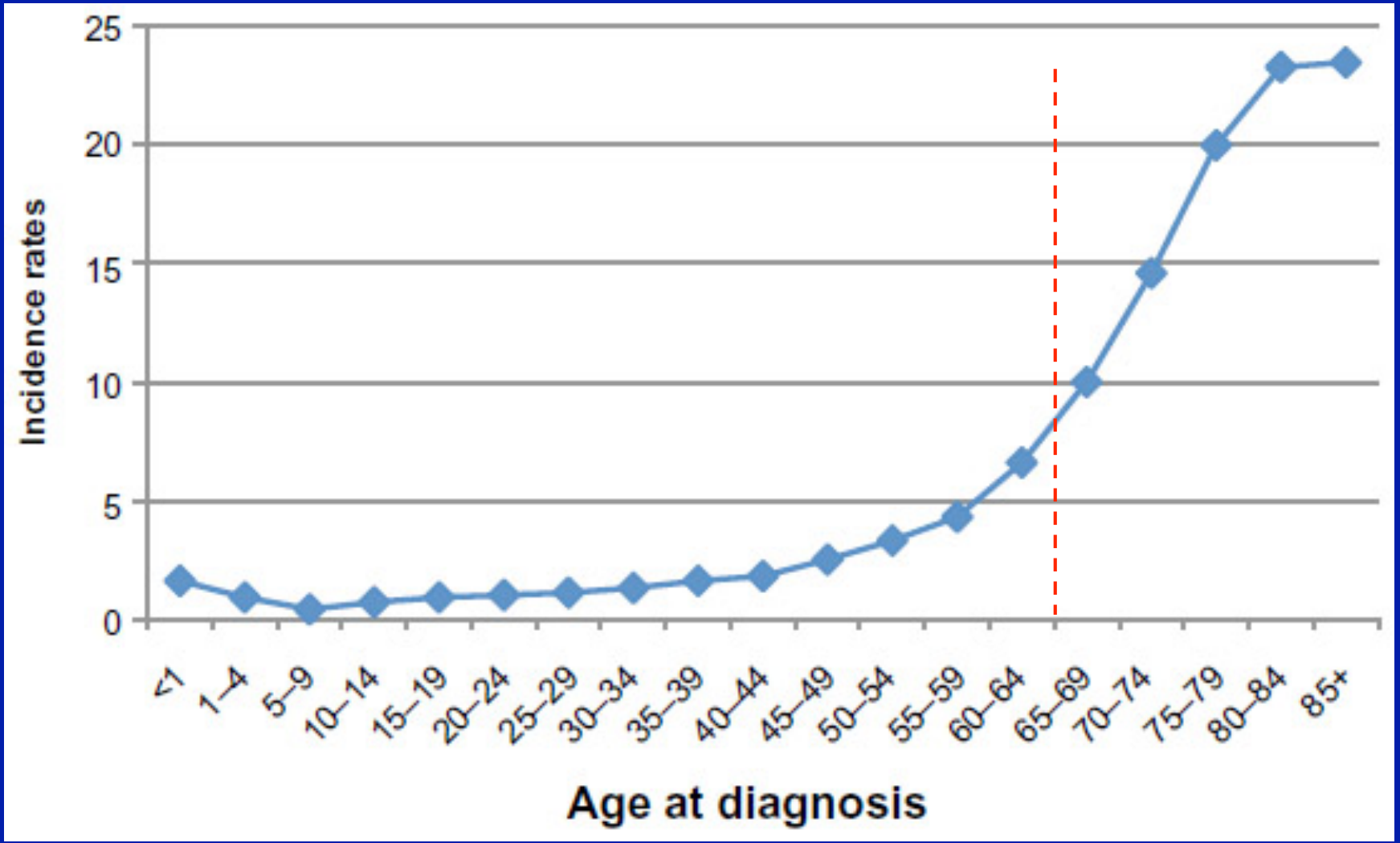
Aging is not a battle, it's a massacre.

Phillip Roth

Age and Cancer Risk



Age distribution of AML



Second or New Cancer

- Shared genetic risk (known and unknown)
- Shared environmental exposure (known and unknown)
- Field *cancerization*
- Increasing age
- Surveillance bias

New Cancers in People with a 1st Cancer

Age at initial diagnosis	Total		
	O	O/E	EAR
All ages	**185,407**	**1.14***	**21**
00–17	351	6.13*	15
18–29	1,401	2.92*	22
30–39	4,909	2.37*	39
40–49	13,537	1.61*	39
50–59	34,159	1.27*	32
60–69	62,286	1.13*	23
70–79	52,321	1.02*	4
80–115	16,443	0.92*	-19

Curtis NCI Monograph

Cancer Risks

Lifetime risk males	43%
Lifetime risk females	39%
2nd Cancer	10-15%

Given this confounding and imprecision we can only estimate whether leukaemia developing after a prior cancer is *therapy-related*.

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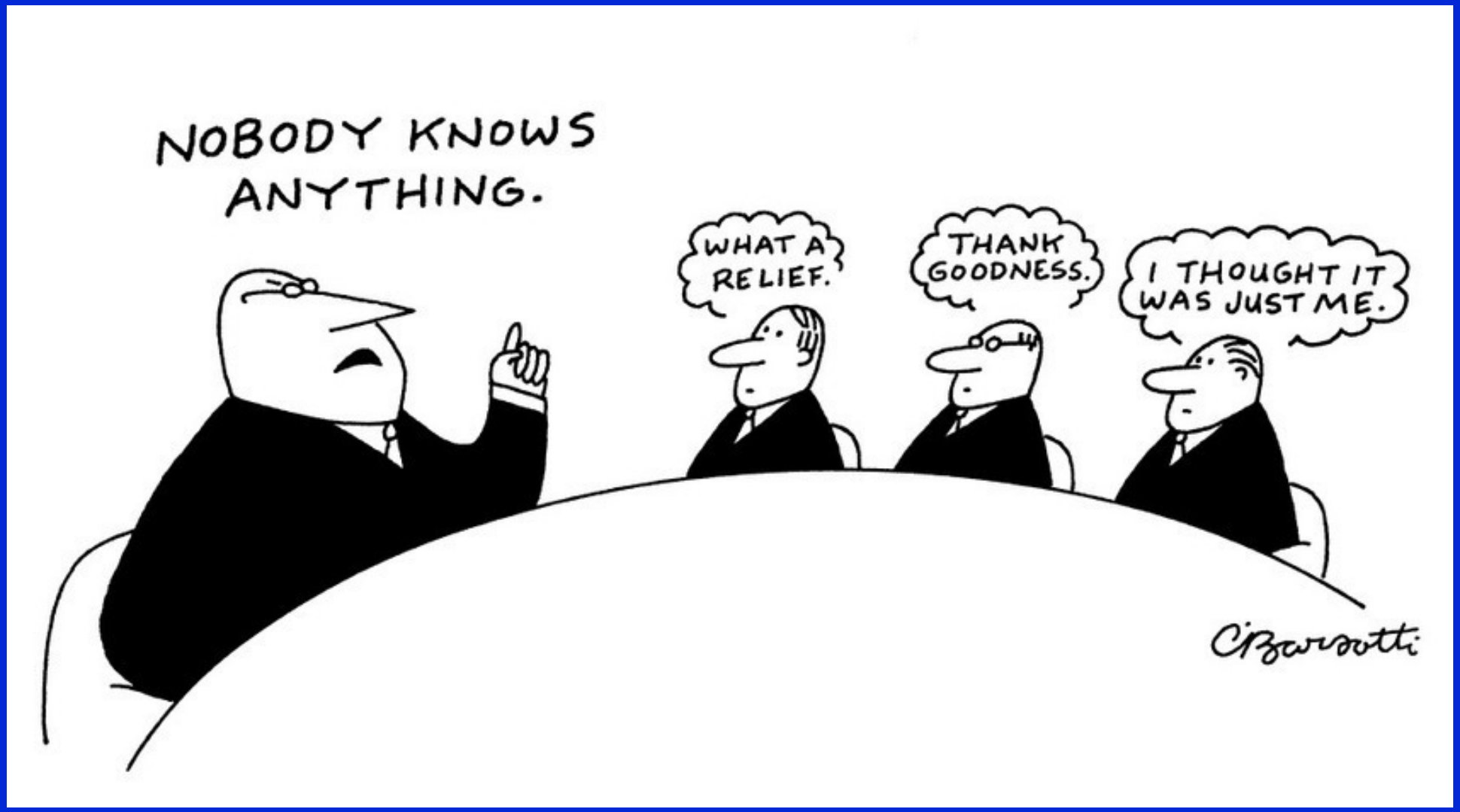
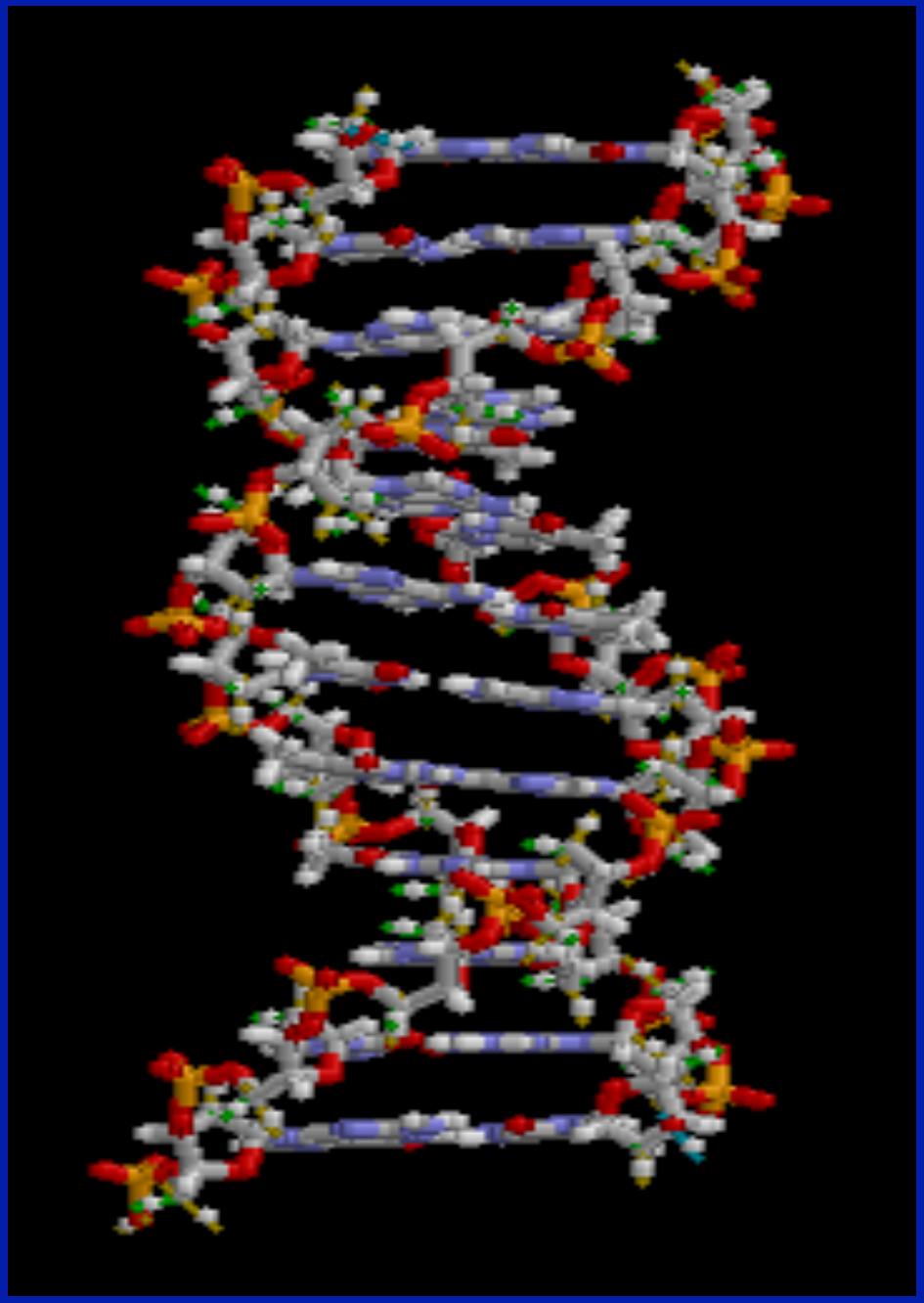

NOBODY KNOWS ANYTHING.
WHAT A RELIEF.
THANK GOODNESS.
I THOUGHT IT WAS JUST ME.

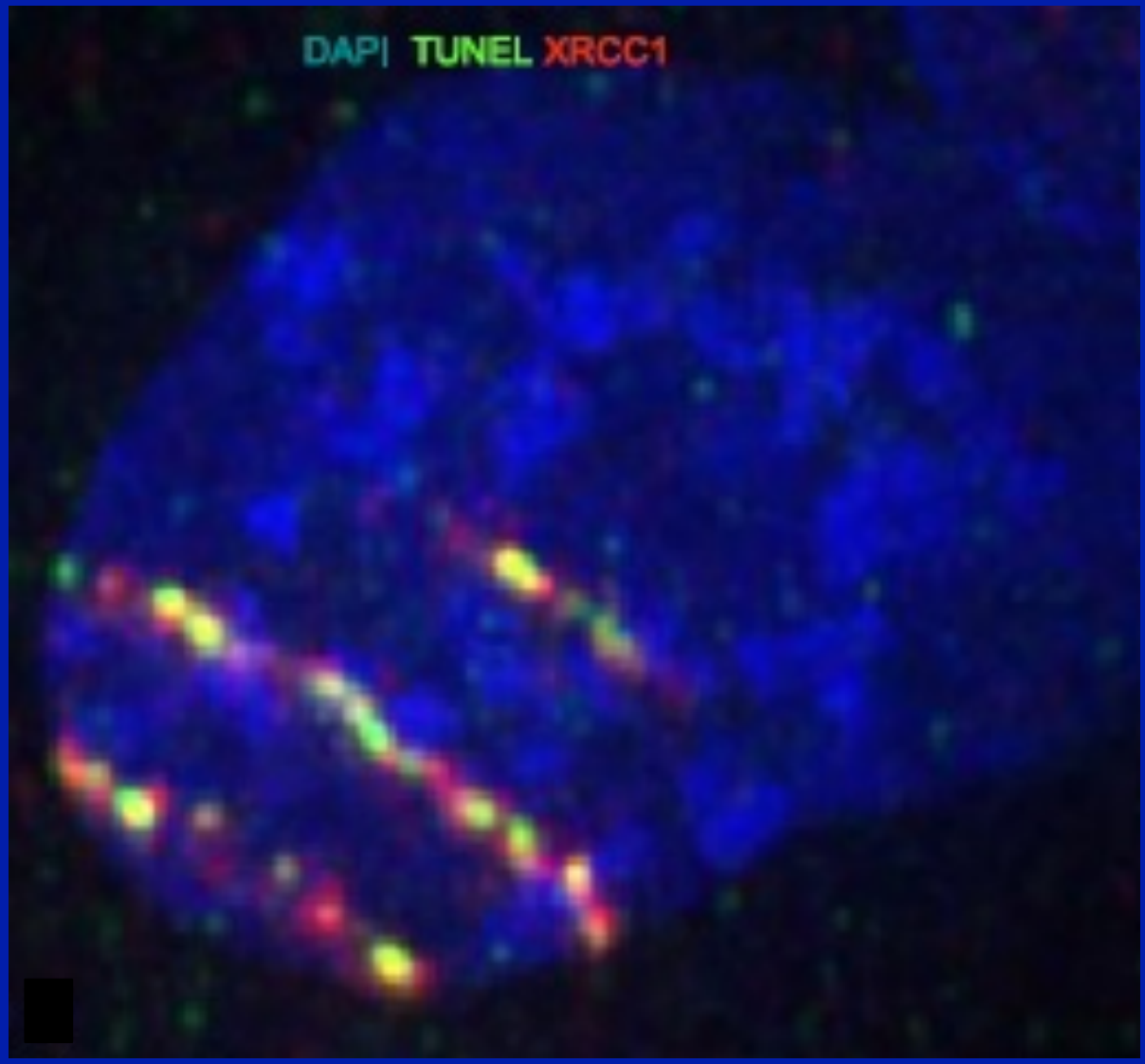
It is uncertain everything is uncertain

Blaise Pascal

Esce dalla porta e rientra dalla finestra

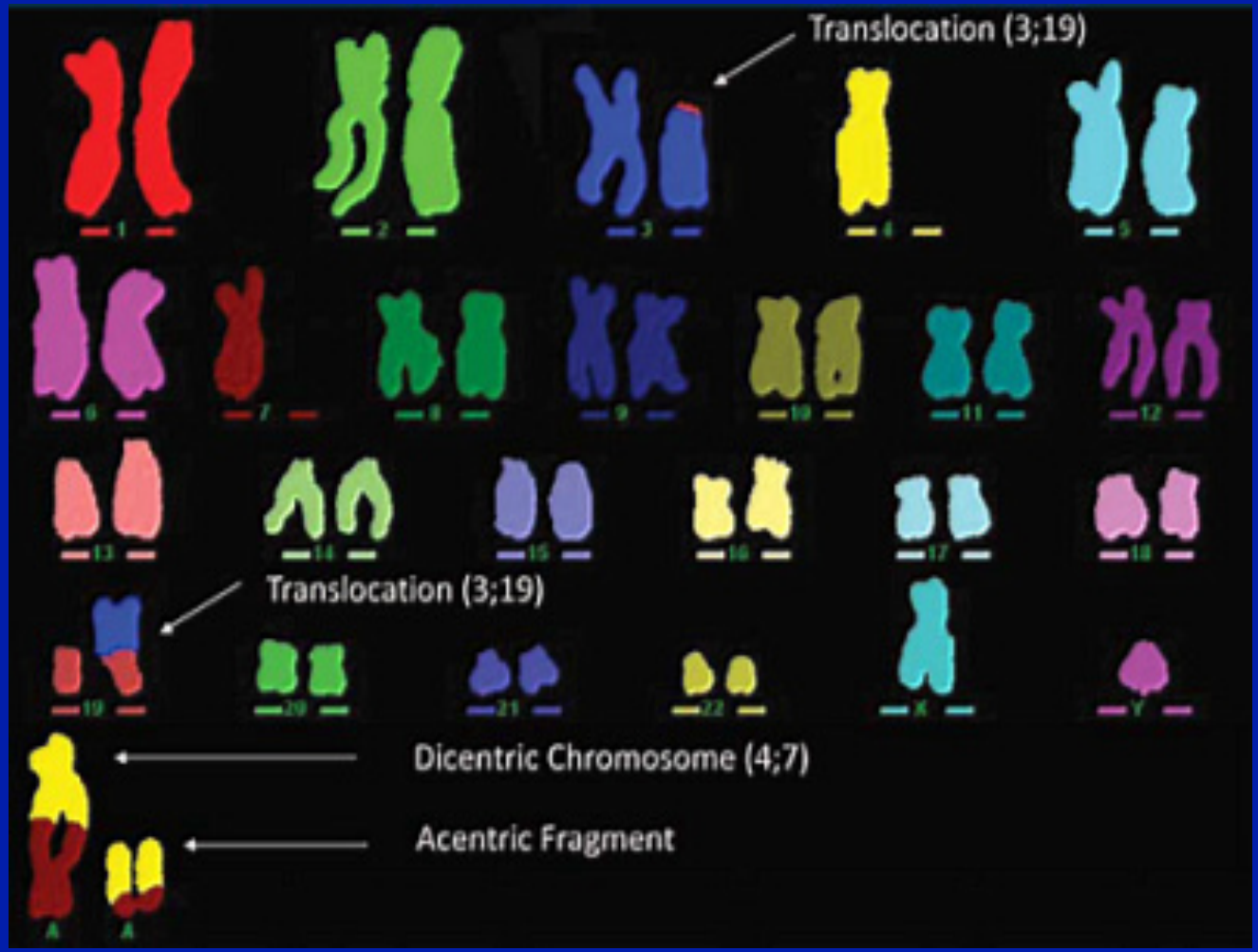


Uranium Ion Paths



Durante Health Phy 2012

1 Gy γ or photon radiation

1000 single-strand breaks
500 damaged bases
40 double-strand breaks
150 DNA-protein cross-links

Radiation-Induced Translocations