

A MODERN BIODOSIMETRIC RE-ASSESSMENT OF THREE MILE ISLAND EXPOSURES USING WHOLE GENOME DIRECTIONAL GENOMIC HYBRIDIZATION (dGH)

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Background and Aim:

The 1979 accident at the Three Mile Island nuclear power station in Pennsylvania was the largest nuclear reactor accident to occur in the Western hemisphere. While the exposure to ionizing radiation suffered by any single individual is believed to have been low, the radiation release was substantial. About 22,000,000 Curies of the radioactive noble gas xenon-133 escaped into the environment. The commission appointed to evaluate the event concluded that the only harm to the population was due to panic and stress. Anecdotal evidence of symptoms consistent with radiation exposure were reported, however, and a limited biodosimetric investigation performed in 1994 produced evidence consistent with significant radiation exposure. Subsequent epidemiological investigations have produced equivocal findings. Could the 1994 finding of severe radiation exposure have been correct?



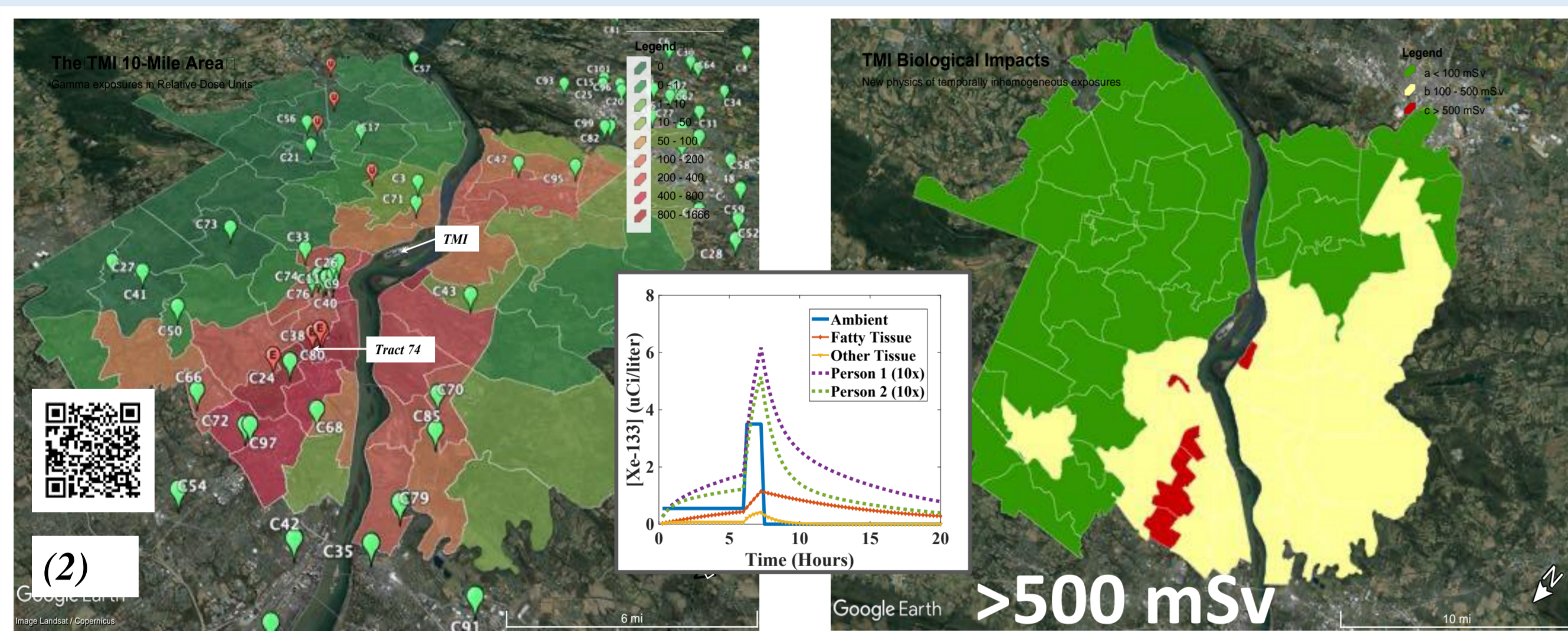
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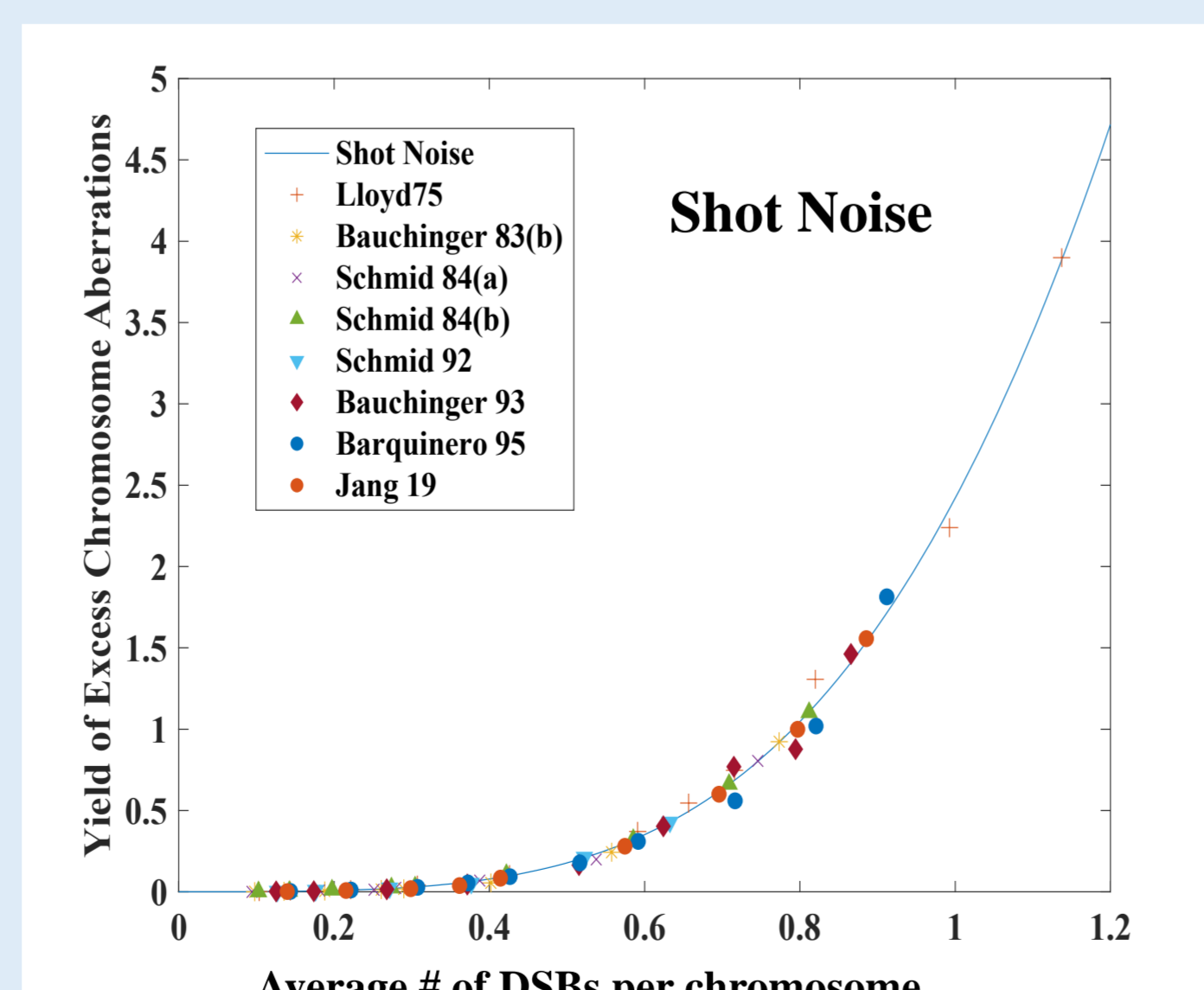
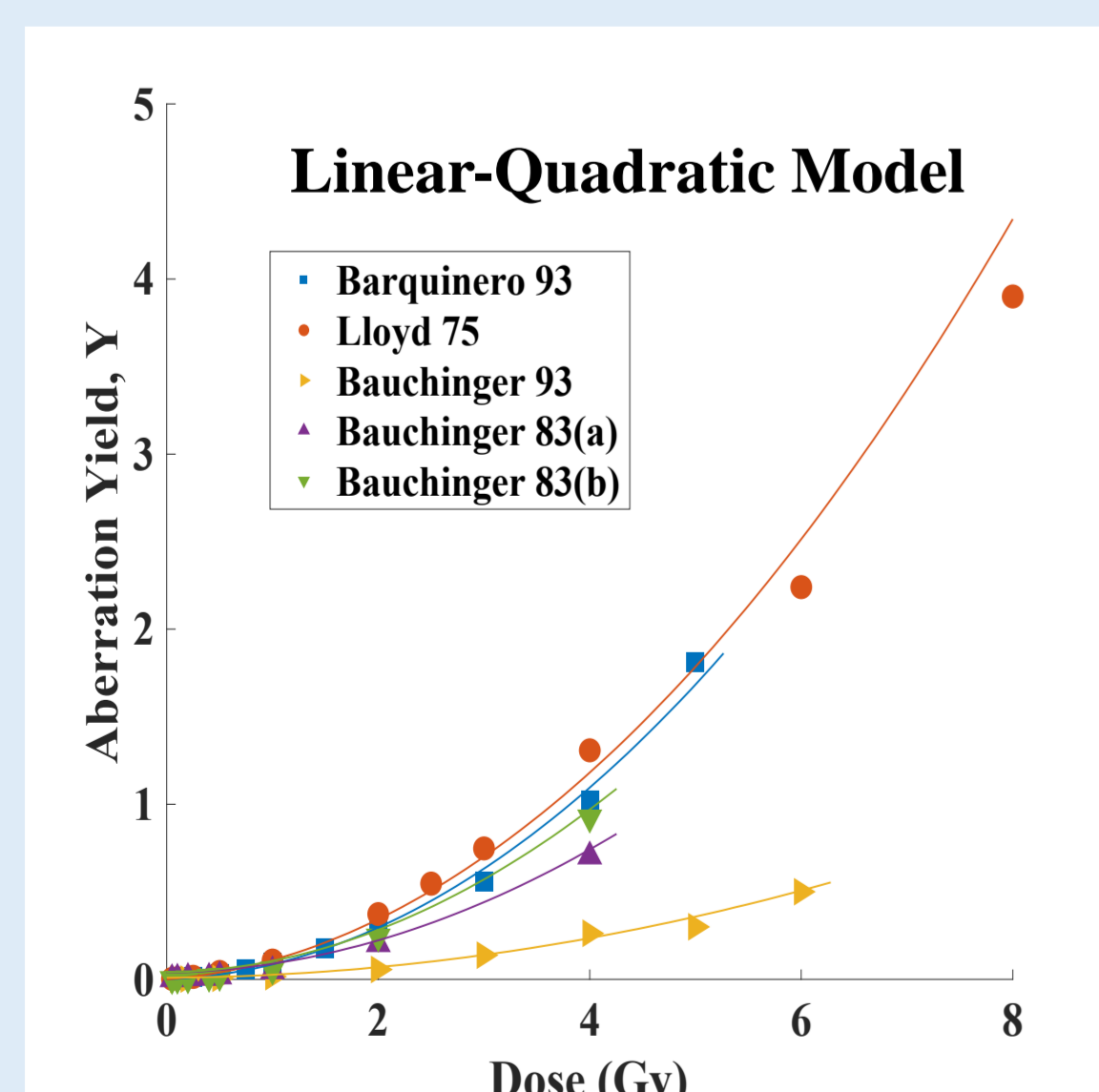
Methods

- We join, for the first time, the recently-proposed physics of radiobiological shot noise with environmental epidemiology.
- Using Whole Genome Directional Genomic Hybridization (dGH), we are testing participant blood samples and measuring inversions and translocations - stable biomarkers of radiation exposure detectable decades after the primary exposure.
- We have so far collected and analyzed eight blood samples, four from persons in the path of the Xe-133 plume on 28-29 March 1979, and four from age-matched individuals living nearby who were not. Four more samples will be collected soon.



Shot Noise

- Interactions between matter and ionizing radiation are stochastic (random). There are well-established rules describing stochastic processes. Only when a "large" number of interactions happen within a short interval of time, is the behavior deterministic.
- The TMI exposures were of long duration (> 20 hours). Shot noise dominates in this case.



- The LQ model is mechanistic. Yet no prediction for α, β coefficients.
- If one understands the characteristics of the source of ionizing radiation, in fact there exists a *universal* curve describing the generation of chromosome aberrations.
- The universal curve accounts for dose rate and the duration of exposure as well.

The Central Paradox

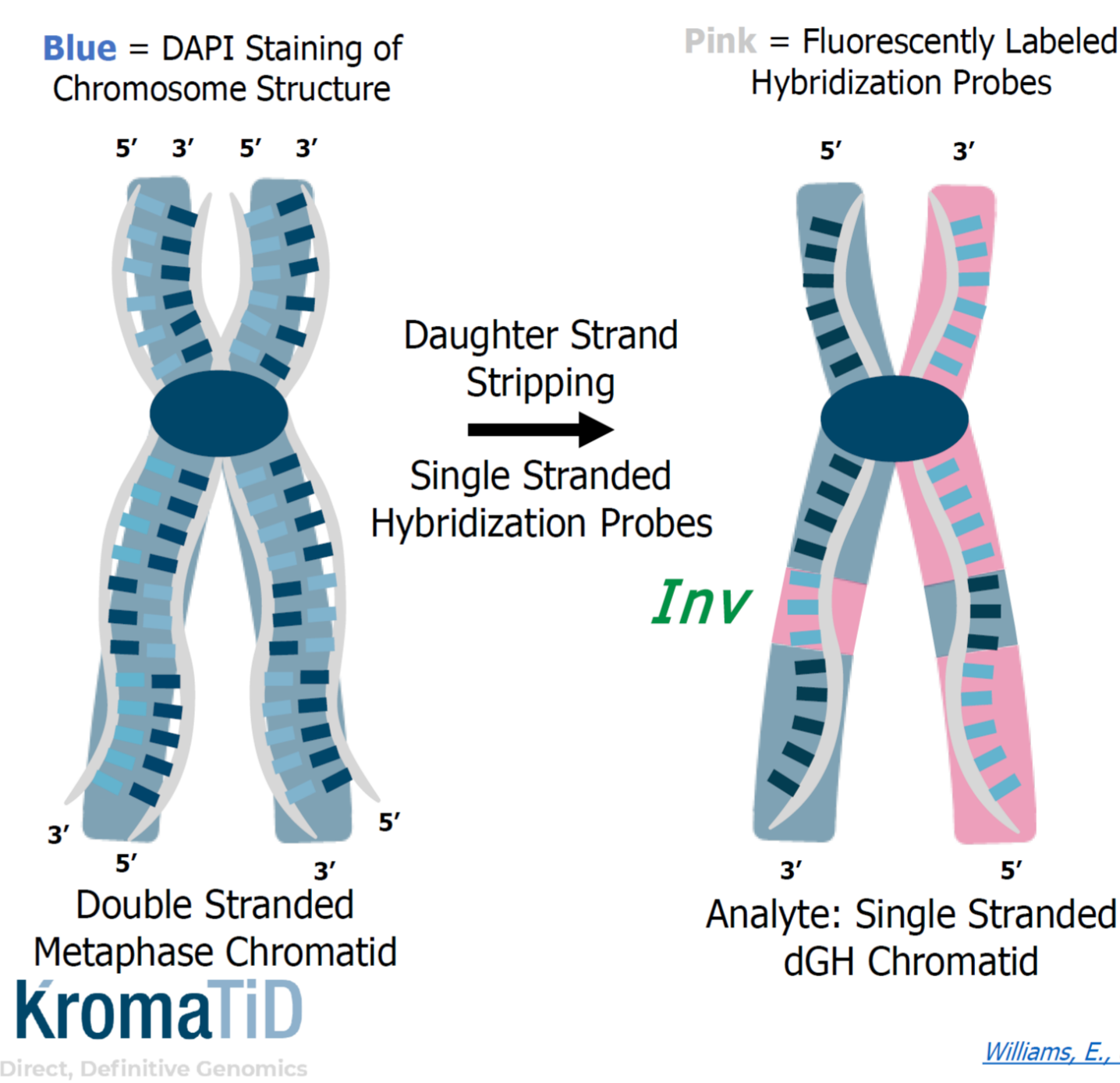
TABLE 1
 Summary of the Results of the Chromosome Aberration Analyses Conducted and Reported by Shevchenko et al. (17, 21, 29) for the Three Mile Island Exposed Group and Subgroup, and the Two Control Groups of Russian Men

(I)	FISH				Dicentric and centric rings			
	No. of persons	No. of cells scored	No. of translocations	Frequency of translocations per 10 ³ cells (95% CI)	Frequency of translocations per 10 ³ genome equivalent (95% CI)	No. of cells scored	No. of dicentrics or centric rings	Frequency of dicentrics and centric rings per 10 ³ cells (95% CI)
Exposed	29	N/A	N/A	N/A	N/A	14,854	30	2.0 (1.4, 2.9)
Exposed subgroup	6	3468	17	4.9 (2.9, 7.8)	15.5 (9.0, 24.8)	3024	14	4.6 (2.5, 7.8)
Control 1	12	13,586	13	1.0 (0.5, 1.6)	3.2 (1.7, 5.5)	N/A	N/A	N/A
Control 2	82	N/A	N/A	N/A	N/A	26,849	5	0.2 (0.1, 0.4)

Notes. The chromosome aberration analyses are for stable translocations derived from fluorescence *in situ* hybridization (FISH) and for unstable dicentrics and centric rings derived from conventional scoring. N/A = not applicable.

- The (gamma ray) dose to any individual was not larger than about 2 mSv, on the order of annual exposure to background radiation.
- Cytogenetic analysis performed in 1994-95 revealed frequencies of chromosome aberrations from 5x (stable) to 10x (unstable) higher than control levels.
- Evidence from personal anecdote, materials analysis, effects on plant life, and immunological examination were consistent with higher levels of radiation exposure.

Biodosimetry with Whole Genome dGH™

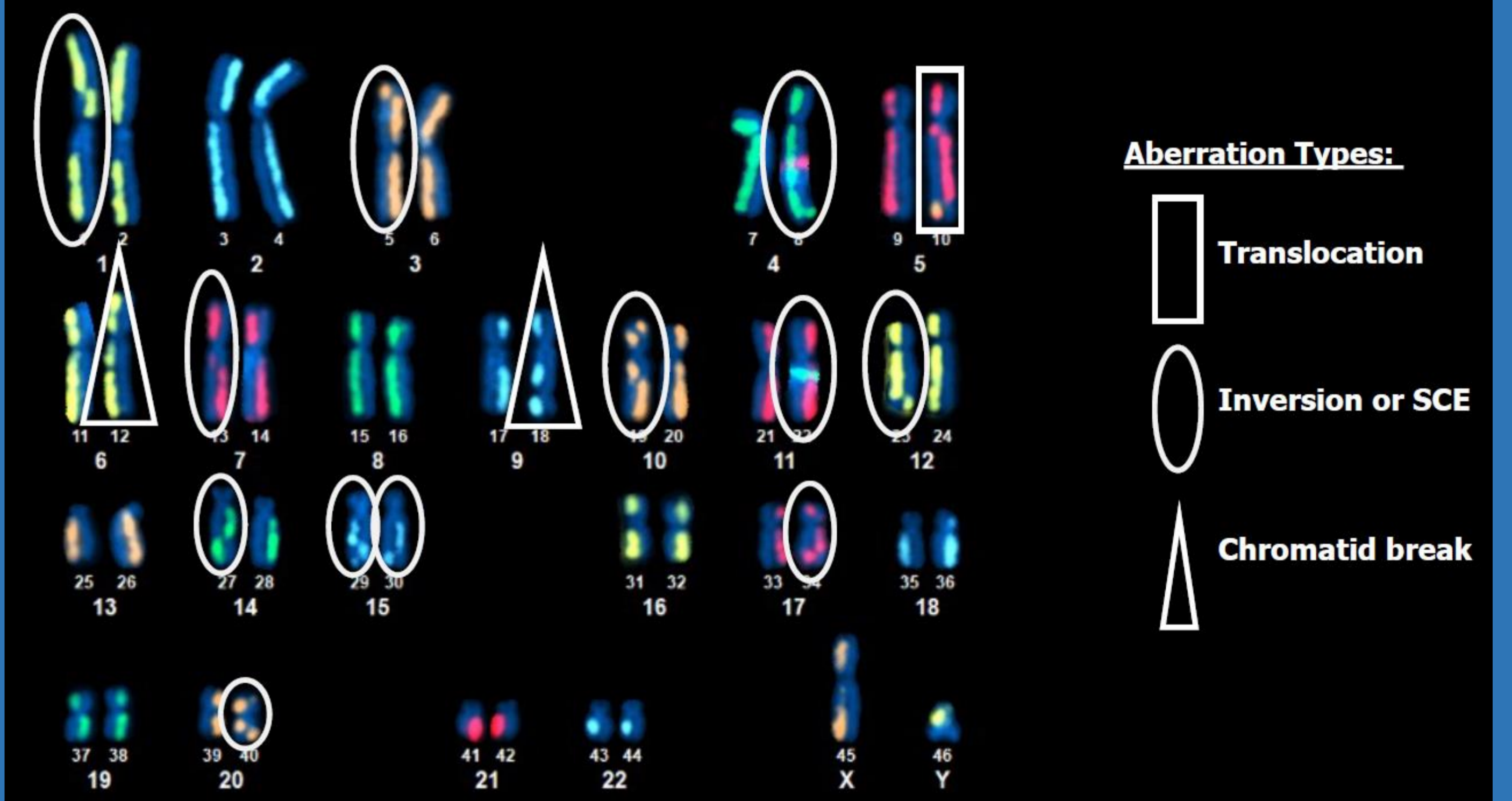


Directional Genomic Hybridization (dGH) is an extremely sensitive method for measuring the mis-repair of radiation induced double strand breaks.

Mis-alignment of these double stranded breaks during DNA repair leads to structural variation, inversions, translocations and deletions.

Radiation induced DNA damage to the Hemopoietic Stem Cells (HSCs) leaves damage signatures in the circulating blood that can be measured by dGH for decades after exposure.

Case Study: Un-Sequenceable Rearrangements



Results and Conclusions:

Examples of rearrangements detectable by dGH. Due to the small sample size thus far, we cannot consider differences in chromosomal aberrations between exposed and unexposed individuals. The feasibility of a larger investigation with adequate statistical power, however, has been demonstrated.

References:

(1) Little MP, Wakeford R, Hatch M, Ainsbury EA, Tawn EJ. Chromosome Aberrations in a Group of People Exposed to Radioactive Releases from the Three Mile Island Nuclear Accident and Inferences for Radiation Effects. *Radiat Res.* 2021 Jun 1;195(6):584-589. doi: 10.1667/RADE-21-00046.1. PMID: 33788925; PMCID: PMC8244829.

(2) Datesman, A.M. Radiobiological shot noise explains Three Mile Island biodosimetry indicating nearly 1,000 mSv exposures. *Sci Rep* 10, 10933 (2020). <https://doi.org/10.1038/s41598-020-67826-5>

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