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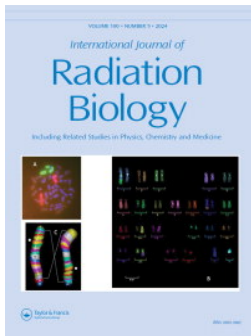
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Consideration of hereditary effects in the radiological protection system: evolution and current status

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ABSTRACT

Purpose: The purpose of this paper is to provide an overview of the methodology used to estimate radiation genetic risks and quantify the risk of hereditary effects as outlined in the ICRP Publication 103. It aims to highlight the historical background and development of the doubling dose method for estimating radiation-related genetic risks and its continued use in radiological protection frameworks.

Results: This article emphasizes the complexity associated with quantifying the risk of hereditary effects caused by radiation exposure and highlights the need for further clarification and explanation of the calculation method. As scientific knowledge in radiation sciences and human genetics continues to advance in relation to a number of factors including stability of disease frequency, selection pressures, and epigenetic changes, the characterization and quantification of genetic effects still remains a major issue for the radiological protection system of the International Commission on Radiological Protection.

Conclusion: Further research and advancements in this field are crucial for enhancing our understanding and addressing the complexities involved in assessing and managing the risks associated with hereditary effects of radiation.

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Introduction

In 1927, Muller made a significant breakthrough by reporting that exposure to X-rays can induce observable genetic changes in the fruit fly, *Drosophila melanogaster*. These included notable mutations in eye color, ebony, ‘vestigial wing’, and the recessive lethal mutation. This discovery, for which he received the Nobel Prize for Medicine in 1946, fueled scientific controversies over decades (Muller 1955; Hamblin 2007) and had a profound impact on the public’s perception of radiological risk worldwide (Zölzer et al. 2023).

However, the genetic effects of exposure to ionizing radiation did not receive much attention until the detonation of the atomic bombs over Hiroshima and Nagasaki during World War II in 1945.


The subsequent irradiation of the affected populations raised widespread concerns about the potential adverse health effects associated with the exposure of a large number of individuals to low doses of radiation. Furthermore, the

concern about radiation risks continued to grow with the extensive atmospheric nuclear weapon testing in the late-1950s and early-1960s. One notable example is the Bikini test in the Marshall Islands, code-named ‘BRAVO,’ which resulted in significant fallout over the atolls of Rongelap and Rongerik, as well as the Japanese fishing vessel known as the Fukuryu Maru (Lucky Dragon) (Sankaranarayanan and Wassom 2008).

The existence of a genetic effect of exposure to ionizing radiation has been evident in mouse studies as early as the 1950s (Russell et al. 1958). However, while animal experiments clearly demonstrate that radiation can induce mutations, it is not clear that radiation induces any specific hereditary effects, but rather that it can potentiate effects that occur without radiation exposure.

In humans exposed to ionizing radiation, despite several key epidemiological studies in this area, no radiation-related genetic diseases have been reliably demonstrated (United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) 2001; Yeager et al. 2021). Especially,

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no radiation-related genetic diseases have been consistently demonstrated on the children of parents exposed to ionizing radiation during the explosions of the atomic bombs over Hiroshima and Nagasaki by the genetic study at the Radiation Effects Research Foundation (RERF, initially called 'Atomic Bomb Casualty Commission' (ABCC)) (Otake et al. 1990; Neel and Schull 1991; Ozasa et al. 2018).

Nonetheless, given that ionizing radiation can cause mutations, and that those mutations are linked with a number of different health consequences, in the mid-1950s, genetic effects were considered in radiological protection recommendations (Sankaranarayanan and Wassom 2008). Thus, the International Commission on Radiological Protection (ICRP), considering the lack of agreement regarding the risk of genetic damage from radiation, adopted an amendment in 1956 to its general recommendations (Clarke and Valentin 2009) stating that *'it was prudent to limit the dose of radiation received by gametes from all sources additional to the natural background to an amount of the order of the natural background in the regions of the earth at present inhabited'*. Also, in the 1970s the concept of radiation detriment was introduced in the ICRP radiological protection system to quantify the risk of stochastic effects, including, from the outset, the risk of hereditary effects (International Commission on Radiological Protection (ICRP) 1977). Numerical risk estimates evolved over time, but hereditary effects have always been considered in the calculation of radiation detriment, up to the last recommendations in 2007 (International Commission on Radiological Protection (ICRP) 2007). Due to the limited evidence of radiation-related genetic diseases in humans, the methodologies developed and employed to estimate the risk of hereditary effects since the mid-1950s have relied on indirect approaches and based on the best use of mutation data obtained in radiation studies with mice (Sankaranarayanan and Wassom 2008).

Today, there remains a lack of consistent evidence demonstrating radiation-related genetic diseases within human populations (Ozasa et al. 2018). A recent reassessment of the A bomb survivor data suggested an association between parental exposure to radiation and an increased risk of major congenital malformations and perinatal death, but the estimates were imprecise, and most were not statistically significant (Yamada et al. 2021). An updated review of the epidemiological literature is published in the same issue of the International Journal of Radiation Biology (Amrenova et al. 2023; Stephens et al. 2023).

While large uncertainties remain, scientific understanding of radiation-related hereditary effects continues to advance, in relation to a number of factors including stability of disease frequency, selection pressures, human genetics and epigenetics. As such and given the process of review and revision of the system of radiological protection launched by ICRP (Clement et al. 2021; Laurier et al. 2021), it appeared important to make clear how the risk of hereditary effects is currently calculated and integrated in the calculation of the ICRP radiation detriment.

According to Visscher et al. (2008), 'Heritability allows a comparison of the relative importance of genes and environment to the variation of traits within and across populations'. In the radiation field, the terms 'genetic diseases', 'heritable effects' and 'hereditary effects' have been used over time to express 'the probability of harmful genetic effects that manifest in the descendants of a population that has sustained radiation exposures' (ICRP 2007). While the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) always used the term 'hereditary' (UNSCEAR 2001), ICRP used both 'heritable' and 'hereditary' terms; (ICRP 2007). Hereditary effects have also been denominated as 'effects of pre-conceptional radiation exposure'. In this article, we decided to use the term 'hereditary effects', with the following definition that they are "radiation-related health effects that are caused by DNA damage of gametes and that manifest in a descendant of the exposed person" (ICRP 2021).

The aim of this article is to describe how the risk of hereditary effects associated with exposure to ionizing radiation is calculated in the ICRP Publication 103 (ICRP 2007). The method of calculation is described, and the justification, data source, and evolution over time of each of the parameters involved in the calculation are explained. The limits and advantages of this approach are discussed.

Categories of hereditary diseases considered in radiological protection

Hereditary diseases have generally been classified as Mendelian, chromosomal or multifactorial. Note that since ICRP Publication 103, chromosomal diseases have been grouped together with autosomal dominant and X-linked diseases (ICRP 2007).

Mendelian diseases

The category of Mendelian diseases (also denominated as 'monogenic diseases' or 'single-gene diseases') includes disorders resulting from mutations that occur in single genes. These diseases are further classified into autosomal dominant, autosomal recessive, and X-linked recessive based on the chromosomal location of the mutated genes and their transmission patterns:

- Autosomal dominant: the mutation of a gene in one parent is, if inherited, sufficient to induce the disease in offspring,
- Autosomal recessive: the mutation of a gene has to be present in both parents (inherited or new mutations) and both mutated alleles have to be inherited from both parents to induce the disease in offspring,
- X-linked recessive: the chance of onset of disease depends on the sex of the offspring (it occurs essentially in males where the X chromosome is haploid) and whether father or mother (or both) are carrier of the mutation.

Mendelian disorders include for example achondroplasia, neurofibromatosis, Marfan syndrome, cystic fibrosis, haemochromatosis, Bloom syndrome, ataxia telangiectasia, hemophilia, Duchenne muscular dystrophy, Fabry disease, and Rett syndrome (UNSCEAR 2001).

Chromosomal diseases

Chromosomal diseases occur due to significant numerical changes (e.g., Down syndrome due to trisomy for chromosome 21) or structural abnormalities of chromosomes (e.g., Cri du chat syndrome due to deletion of part or whole short arm of chromosome 5) typically detectable through cytological examinations of cells. This is not an etiological category and, further, deletions (microscopically detectable or not) are now known to contribute to a number of genetic diseases grouped under autosomal dominant, autosomal recessive and X-linked diseases. Within the framework of ICRP Publication 103, the risk of chromosomal diseases has been assumed to be subsumed under the risk associated with autosomal dominant and X-linked diseases (ICRP 2007).

Multifactorial diseases

The class of multifactorial diseases (or ‘complex diseases’) includes human genetic diseases that are believed to arise as a result of a complex interplay between genetic and environmental factors. It subdivides into diseases due to common congenital abnormalities that are present at birth and chronic diseases which manifest in later life.

Unlike Mendelian diseases, multifactorial diseases do not exhibit consistent or recognizable inheritance, and mechanisms by which the genes and the environment interact to cause these conditions are largely unknown. (Ruderfer et al. 2010). Family and twin studies provide compelling evidence of a genetic component in the etiology of these diseases, as they consistently demonstrate a higher disease risk among first-degree relatives of affected individuals compared to matched controls. One of the models utilized to explain the inheritance patterns of multifactorial diseases and assess the disease recurrence risks in relatives is the multifactorial threshold model (MTM) of disease liability (ICRP 2007).

Congenital abnormalities

According to the definition provided by UNSCEAR, congenital abnormalities are structural defects, either gross or microscopic, that are present at birth, regardless of whether they are detected at that time. The term ‘congenital’ signifies their presence at birth and has no etiological connotation. These abnormalities arise due to dysmorphogenesis and can occur as isolated or multiple defects. Isolated congenital abnormalities can be attributed to localized errors in morphogenesis, while multiple congenital abnormalities result from two or more distinct errors during the development of an individual (UNSCEAR 2001).

Most frequent congenital abnormalities concern the musculoskeletal system, the urogenital system, the heart and circulatory system, the digestive system and cleft lip with/without cleft palate. A small proportion of congenital abnormalities show Mendelian transmission. For instance, cleft lip with or without cleft palate can be associated with autosomal dominant conditions. Additionally, various chromosomal abnormalities and fetal alcohol syndrome have been linked to congenital cardiovascular malformations (UNSCEAR 2001).

Chronic diseases

Chronic diseases may or may not develop in individuals, depending on the presence or absence of risk factors, which can be genetic or environmental in nature. Therefore, the concepts of ‘genetic susceptibility’ and ‘risk factors’ are appropriate for understanding these diseases. For example, elevated serum cholesterol levels are recognized as one of the risk factors for coronary heart disease, elevated blood pressure for stroke, and elevated blood sugar levels for diabetes (Jousilahti et al. 1998; O’Donnell et al. 2010).

Chronic diseases include especially common adult diseases, such as diabetes type II, coronary heart disease and essential hypertension. The list of diseases to determine hereditary risk includes a total of 26 very diverse disorders with possible genetic background, such as affective psychoses, varicose veins of lower extremities, allergic rhinitis, asthma, peptic ulcer, rheumatoid arthritis, or juvenile osteochondrosis of the spine (Czeizel et al. 1988; UNSCEAR 2001) (See Supplemental Table S1).

Our current understanding of multifactorial diseases is still limited regarding the genes involved, their number, the types of mutational alterations and the nature of environmental factors. Data from well-studied chronic diseases such as essential hypertension, diabetes, and coronary heart disease, permit one to conceptualize the relationships between gene mutations and multifactorial diseases. Genetic susceptibility to developing a multifactorial disease is attributed to two categories of genes: ‘polygenes’ or ‘low penetrance genes’ where mutant alleles have modest to moderate effects on the risk factor trait, and ‘major genes’ where mutant alleles have strong effects (ICRP 1999; Scott and Lee 2020). Since polygenes are more common, they contribute significantly to the variation of risk factor traits in the population at large. In contrast, mutations in major genes, although having a devastating effect at the individual level, are rare and hence contribute less to the variability of risk factor traits.

Calculation of radiation-related risk of hereditary disorders

Genetic risk estimation approach

The UNSCEAR 2001 Report provides estimates of genetic risks expressed as the predicted number of additional cases (i.e., above the baseline) of different classes of genetic disease per 100 live births per Gy for a population exposed to low-LET, low-dose exposure, generation after generation (UNSCEAR 2001). Using these estimates, ICRP derived risk assessments for different types of genetic diseases [Tables A.6.4 and A.6.6, *Publication 103* (ICRP 2007)].

Due to the limited evidence for radiation-related genetic diseases in humans, the methods developed and utilized since the mid-1950s have relied on indirect approaches and based on the best use of mutation data obtained in radiation studies with mice, data on baseline frequencies of genetic diseases in the population (based on mice, and then on human data since 2001), and population genetic theory to predict the radiation risk of genetic diseases in humans. One established method used since the early 1970s is the doubling dose method, which was employed by ICRP in its Publication 60 (ICRP 1991) to assess the risk of hereditary effects. This method enables one to express the expected increase in the frequencies of genetic diseases in terms of their baseline frequencies using Equation (1):

$$\text{Risk per unit dose} = P \times [1/DD] \times MC \quad (1)$$

With

- P: baseline frequency of the genetic disease class
- DD: doubling dose (required amount of radiation which produces the same rate of new mutations as would occur spontaneously in a generation)
- MC: disease-class-specific mutation component (relative increase in disease frequency per unit relative increase in mutation rate)

In its 2007 recommendations, ICRP mentioned several scientific advances (ICRP 2007), based on the UNSCEAR report 2001 (UNSCEAR 2001), that have been made since the previous recommendations (ICRP 1991) including:

- Revision of the estimates of the baseline frequencies (P) of Mendelian diseases;
- Introduction of a conceptual change in the calculation of the DD (i.e., use of human data on spontaneous rates and of mouse data on induced mutation rates);
- Elaboration of methods for estimating MC for Mendelian and chronic diseases.

In the ICRP Publication 103 (ICRP 2007), an important aspect is the inclusion of the 'potential recoverability correction factor' (PRCF) in the equation to bridge the gap between the rates of radiation-induced mutations in mice and the risk of radiation-related genetic disease in human live births. Furthermore, the publication introduces the concept that the adverse effects of radiation-related genetic damage in humans are likely to manifest predominantly as multisystem developmental abnormalities in the progeny.

Then in ICRP Publication 103, the risk of genetic diseases is calculated according to Equation (2):

$$\text{Risk per unit dose} = \sum_D P_D \times \left[\frac{1}{DD_D} \right] \times MC_D \times PRCF_D \quad (2)$$

With

- D: class of diseases
- PRCF: potential recoverability correction factor

It has to be noted that Equation (2) doesn't apply to the risk of congenital abnormalities, which is estimated from mouse data, without recourse to the DD method (Sankaranarayanan and Wassom 2008). Their risk is expressed as the number of genetic diseases in a number of progeny (or live births) per Gy (ICRP 2007).

Baseline frequencies (P)

The baseline disease frequency P is the number of naturally occurring cases of diseases with a distinct mutational background. Regarding the mutation/selection equilibrium theory used to estimate the hereditary effect, the baseline mutation frequency corresponds to the initial equilibrium incidence without radiation exposure (except background radiation).

As shown in Table 1, the baseline disease frequency is estimated separately for Mendelian diseases (Trimble and Doughty 1974), chromosomal diseases (UNSCEAR 1977), congenital diseases (Czeizel and Sankaranarayanan 1984) and chronic diseases (Czeizel et al. 1988). In ICRP Publication 103, the baseline disease frequencies published in 2001 by UNSCEAR (UNSCEAR 2001) are used. They are the same as those published by UNSCEAR in 1993 (UNSCEAR 1993), except for Mendelian diseases, which were updated.

Mendelian diseases

Baseline disease frequencies for Mendelian diseases were estimated by Carter in 1977 who used the method of estimating the baseline frequency indirectly by using incidence or prevalence data from human studies on the different diseases. For diseases with an immediate onset after birth the incidence can be used directly; this is not feasible for diseases with an onset in childhood or adulthood. To estimate the birth frequency for a disease with late onset, prevalence data can be used. The prevalence is multiplied with the mean life-expectancy of the population at birth and divided by the mean duration of clinical illness (mean age at death minus mean age at clinical onset) (Carter 1977).

For autosomal dominant diseases, Carter estimated the birth frequency for 12 'common diseases' (prevalence > 1 per 10⁴ births) and 13 'less common diseases' (prevalence 0.1-1 per 10⁴ births). For autosomal recessive and for X-linked, 8 diseases and 4 diseases with a prevalence >1 per 10⁴ births were used, respectively. The baseline frequencies reported by Carter were 63 diseases per 10⁴ births for

Table 1. Baseline frequencies of genetic diseases in human populations in UNSCEAR reports.

Class of Disease	Baseline frequencies per 100 live births	
	UNSCEAR 1993	UNSCEAR 2001
Mendelian		
Autosomal dominant	0.95	1.50
X-linked	0.05	0.15
Autosomal recessive	0.25	0.75
Chromosomal	0.40	0.40
Multifactorial		
Congenital abnormalities	6.00	6.00
Chronic diseases	65.00	65.00

autosomal dominant diseases, 17 per 10^4 births for autosomal recessive and 8 per 10^4 births for X-linked for male (4 per 10^4 births for both sexes). He concluded that taking account of underestimation, 100 per 10^4 livebirths seems an appropriate estimate for the overall baseline frequency (with 70 per 10^4 for autosomal dominant, 25 per 10^4 for autosomal recessive and 4 per 10^4 for X-linked) (Carter 1977).

Sankaranarayanan updated and extended the results of Carter. For his analyses, Sankaranarayanan investigated 50 autosomal dominant Mendelian diseases and estimated a disease frequency of 97 to 102 per 10^4 live births. For autosomal recessive conditions, 27 diseases were used summing to a baseline frequency of 52-54 per 10^4 births. For 17 X-linked diseases a disease frequency of 17.8 per 10^4 for males and 8.9 per 10^4 for both sexes were estimated (Trimble and Doughty 1974).

Sankaranarayanan furthermore stated that at the time of the analysis in the 1990s, the Online database Mendelian Inheritance in Men (OMIM) listed 2674 genes for autosomal dominant conditions, 2508 for autosomal recessive conditions and 314 X-linked, that only 10% of the human genome has been sequenced and that the human genome was estimated to contain about 80,000 genes (Sankaranarayanan 1998). Based on these assumptions an upward adjustment of the birth frequency estimates was performed to give 150 per 10^4 for autosomal dominant conditions, 75 per 10^4 for autosomal recessive and 15 per 10^4 for X-linked, which are the final numbers used in the UNSCEAR report 2001 (UNSCEAR 2001) and ICRP Publication 103 (ICRP 2007) (see Table 1).

Chromosomal diseases

In UNSCEAR 2001, the numbers for the baseline frequency of chromosomal diseases from UNSCEAR 1977 were used. The main source of data for UNSCEAR 1977 was the British Columbia Survey on the frequency of live-born individuals affected by hereditary defects and diseases (Trimble and Doughty 1974). However, this study showed some relevant shortcomings, leading to lower results than in comparable studies and the previously used numbers of UNSCEAR 1962 and UNSCEAR 1966.

After reviewing all relevant data and realizing ad-hoc estimations of the possible underestimations, UNSCEAR decided to use an estimate of 0.4 per 100 live-born, which was similar to the previously used (0.42 per 100 live-births) and twice as large as the results of the British Columbia study (see UNSCEAR 1977 Annex H, Table 9).

Congenital abnormalities

Baseline frequency for congenital diseases in UNSCEAR 2001 is based on Czeizel et al. (1984). In this paper, Czeizel et al. evaluated the prevalence of congenital abnormalities in live- and stillbirths in Hungary. In Hungary, reporting of congenital abnormalities is mandatory since 1962 and autopsy of all dead infants is mandatory, too. All data are collected in the Hungarian Congenital Malformation Registry and classified by the International Classification of Diseases. The paper focused on 'major abnormalities' defined as congenital abnormalities with clinical or cosmetic consequences. The overall

calculated prevalence of congenital abnormalities was 597.4 per 10^4 livebirths and 735.9 per 10^4 overall births. In the UNSCEAR report 2001, the rounded prevalence of 6 per cent livebirths was used as baseline frequency (UNSCEAR 2001).

Chronic diseases

Baseline frequencies for chronic diseases in UNSCEAR 2001 are based on Czeizel et al. (1988). The goal of the study was to estimate the health impact of genetically mediated diseases on public health, so the 26 diseases used were chosen by their possible genetic background (See Supplemental Table S1). All data used to calculate the baseline frequency and the mortality rates are from the Hungarian population. The calculation of the prevalent cases was realized by multiplying the age-standardized prevalence rate to the population size at the time of the study. This must be seen critically, because in the primary study, most patients had more than one disease, with on average 2.7 diseases per patient. The earlier shown multiplication with the population size is therefore only a crude measure for the number of expected diseases in the population, but not for the number of affected persons, and should not be used as such. The estimated frequency of the diseases was 6.541 per 10^4 for the Hungarian population and comparable to data from other studies at this time, although the authors report large differences in single entities, leading to the number of 65 per 100 live births used in UNSCEAR 2001.

The baseline frequencies used for risk estimation in ICRP (2007) are based on those from (UNSCEAR 2001). Table 1 presents the baseline frequencies (P) published in UNSCEAR (2001), together with those from (UNSCEAR 1993).

Doubling dose (DD)

The DD is defined as the absorbed dose to the reproduction organs that is required to produce as many hereditary mutations as those arising spontaneously in a generation (Sankaranarayanan and Chakraborty 2000b).

The concept of DD was initially formulated by Muller in the 1950s and evolved over time since then (Sankaranarayanan and Chakraborty 2000b). Table S1 presents the evolution of the concept and estimated values of DD up to the last ICRP recommendations in 2007. Until the 1993 UNSCEAR report (UNSCEAR 1993), DD was estimated to 1 Gy and was based entirely on mouse data on spontaneous and induced rates of recessive mutations in seven genes.

At the beginning of the year 2000, it appeared that the assumption of similar spontaneous mutation rates in mouse and human genes was incorrect. Substantial differences were discovered, particularly in humans, where mutation rates varies between sexes, being higher in males than in females and increase with paternal age. Further, an additional source of uncertainty in spontaneous mutation rate estimates in mice was uncovered, related to mutations which arise as germinal mosaics and which result in clusters of identical mutations in the following generation. Considering these findings, a more cautious approach was proposed,

suggesting the utilization of human data on spontaneous mutation rates alongside mouse data on induced mutation rates for calculating the DD (Sankaranarayanan and Chakraborty 2000b).

This approach was used in 2001 by UNSCEAR (UNSCEAR 2001). Using available experimental data from male mice, the average rate of induced mutations has been estimated on the basis of locus-specific rates for 34 loci. The rate estimated in this way was $(1.08 \pm 0.30) 10^{-5} \text{ locus}^{-1} \text{ Gy}^{-1}$ for acute X or γ irradiation. Applying a dose-rate reduction factor of 3, the rate for chronic irradiation conditions became $0.36 (\pm 0.10) 10^{-5} \text{ locus}^{-1} \text{ Gy}^{-1}$. The justification for applying a reduction factor of 3 for chronic radiation conditions was derived from experiments on mice conducted at the end of the 1950s (Russell et al. 1958). Large-scale experiments showed a linear increase of the mutation rates in the seven locus test up to 9 Gy given at a very low dose rate over many days. The slope of the dose effect relationship was 3 times less than that after acute single doses. As this dose-rate effect was observed in spermatogonia and in oocytes, it was considered that the radiation effect was on the mutation process itself (Sankaranarayanan and Chakraborty 2000b; UNSCEAR 2001).

In addition, since there has been uncertainty whether mouse immature oocytes would provide a good model for assessing the mutational sensitivity of human immature oocytes to radiation, it was assumed that the sensitivity to radiation-related genetic damage is the same for both sexes. Therefore, the rate estimated for males was taken to be applicable to females (Sankaranarayanan and Chakraborty 2000b; UNSCEAR 2001).

Compared to the average baseline rate, the new estimated DD then became 0.82 Gy (± 0.29). Considering the related uncertainties and the approximations introduced, UNSCEAR suggested the continued use of the 1 Gy estimate in order to avoid the impression of undue precision associated with the fractional value 0.82 (UNSCEAR 2001). In its Publication 103, ICRP supported the UNSCEAR judgment and therefore retained a DD value of 1 Gy (ICRP 2007).

The DD method was not applied to congenital abnormalities (UNSCEAR 2001). It was considered possible to develop a composite estimate of the risk for this class of genetic diseases using mouse data (on skeletal abnormalities, cataracts and congenital abnormalities scored in utero), without recourse to the DD method. However, it is important to note that the type of abnormalities and their effect in mice and humans are different. When the rates estimated for skeletal abnormalities, cataracts and congenital abnormalities are combined, it became $\sim 30 \times 10^{-4}$ per gamete per Gy for acute X-irradiation of males. With a dose-rate reduction factor of 3, the rate for chronic irradiation conditions becomes $\sim 10 \times 10^{-4}$ per gamete per Gy, for irradiation of both sexes the rate estimate becomes twice the above value (i.e., $\sim 20 \times 10^{-4}$ per Gy) (Sankaranarayanan 1999).

Mutation component (MC)

The elements of the basic MC concept were initially incorporated into the radiation genetics literature through the

1972 BEIR report (NRC 1972) and were subsequently considered in the papers of Crow and Denniston (1981, 1985) to assess the responsiveness of multifactorial disease to increases in mutation rate, i.e., for a direct evaluation of the impact of an increase in mutation rate on disease frequency in any generation of interest without the need to first estimate the new equilibrium value. The reason is that, on average, more mutations are inherited from the generations before than occurring in the parents of the child at risk. This way, the MC is a consequence of the mutation/selection pressure of inheritance. The concept, methods for estimation, and algebraic formulations were fully elaborated for both Mendelian and multifactorial diseases in ICRP Publication 83 (ICRP 1999).

Thus, MC provides a measure of how the disease frequencies will increase when the mutation rate is increased. The inclusion of this factor in Equation (2) allows the association between mutation and disease to differ across various categories of genetic diseases.

It is important to highlight that MC for Mendelian diseases is based on the equilibrium theory, which assumes that in the absence of radiation exposures, the population is in a state of equilibrium between mutation and selection (Chakraborty et al. 1998). When the mutation rate is increased due to radiation, the balance between mutation and selection is disturbed; however, it is predicted that the population will eventually reach a new equilibrium between mutation and selection. The rate at which this new equilibrium is reached varies among different types of genetic diseases. So, for example, the transition to the new equilibrium is considerably slower for autosomal recessive diseases compared to autosomal dominant and X-linked diseases (ICRP 2007).

For autosomal dominant and X-linked diseases, the estimated MC value of 0.30 was determined based on the average selection coefficient derived from data on naturally occurring autosomal dominant diseases in the first generation (Sankaranarayanan and Chakraborty 2000a, 2000b).

In the case of autosomal recessive diseases, the MC value in the first generation was considered to be close to zero. This is because an autosomal recessive mutation does not manifest as a disease in the first generation.

For multifactorial diseases, the Finite Locus Threshold Model (FLT) was used to reflect the inheritance of traits controlled by multiple genes (ICRP 1999). The FLT is based on the 5-locus model, but assumes that mutations are induced in all the genes associated with a multifactorial disease (Denniston et al. 1998; ICRP 1999).

Concerning chronic diseases, UNSCEAR (UNSCEAR 2001) selected a value of 0.02 as the best estimate for MC.

MC was not needed for congenital abnormalities as the risk of the diseases of this category was estimated without using DD.

Potential recoverability correction factor (PRCF)

The use of induced mutation rates from mouse studies in risk estimation is likely to result in an overestimation of the

rate at which induced mutations in humans will lead to disease. Given the lack of alternative data, there is a need to bridge the gap between the rates of induced mutations in mice and potentially recoverable induced mutations in humans. To address this, a disease-class specific correction factor, denominated as the 'Potential Recoverability Correction Factor' (PRCF) was introduced (UNSCEAR 2001).

To estimate the potential recoverability of induced mutations, a set of criteria was established based on molecular information on recovered mutations in experimental systems. These criteria were then applied to relevant human genes, taking into account factors such as gene size, organization, function, genomic context (e.g., gene-rich or gene-poor region), spectra of spontaneous mutations in the gene, known deletions in the region including contiguous genes, and mutational mechanisms (UNSCEAR 2001).

In the analysis, a total of 63 human genes were included, and it was found that induced mutations in only 21 of these genes, or approximately one-third, may be compatible with viability and thus potentially recoverable in live births. This fraction of about 0.3 is called the unweighted PRCF. When weighted by the respective incidences of these diseases, the weighted PRCF becomes 0.15. (UNSCEAR 2001).

Considering that autosomal dominants have a significantly higher overall incidence compared to X-linked diseases (1.5% versus 0.15%), the PRCFs for autosomal dominants are more relevant. Consequently, Sankaranarayanan and Chakraborty (2000a, 2000b) proposed the utilization of a PRCF range of 0.15 to 0.30 in Equation (2) to estimate the risk of both autosomal dominant and X-linked diseases.

Since the induced relative mutations do not affect the normal function in heterozygotes, and even large deletions may be recoverable (unless the deletion involves neighboring essential structural genes, resulting in unviability of heterozygotes), induced recessive mutations do not, at least in the first few generations, result in recessive diseases. Therefore, as the MC is close to zero in the first few generations, it was considered that there was no need to estimate PRCF for autosomal recessive diseases (Sankaranarayanan and Chakraborty 2000b; UNSCEAR 2001).

For chronic diseases, UNSCEAR adopted a PRCF range of 0.02 to 0.09 (based on just two loci, and with more loci, would have been even smaller) (UNSCEAR 2001). For congenital abnormalities, no PRCF was estimated (UNSCEAR 2001).

Calculation of risk of hereditary effect per unit of dose

Table 2 summarizes the parameter values used for the calculation of genetic risks in UNSCEAR report 2001 (UNSCEAR 2001) and ICRP Publication 103 (ICRP 2007).

Using Equation (2), and the parameter values from Tables 2 and 3 summarizes the estimated risk of genetic diseases per Gy per 100 live births obtained for the first and second generation, for the different classes of disease (based on Table 3 in Sankaranarayanan and Wassom 2008). For

Table 2. Parameter values used for the calculation of risk of genetic diseases in the UNSCEAR report 2001.

Disease class	p	DD	MC	PRCF
Mendelian	1.65 ^a	1	0.3	0.15 to 0.3
Chronic	65.0	1	0.02	0.02 to 0.09
Congenital abnormalities	6.0	NA	NA	NA

P: baseline disease frequency (per 100 live births^b); DD: doubling dose in Gy; MC: Mutation Component; PRCF: potential recoverability correction factor; NA: not applicable.

^aincludes only autosomal dominant and X-linked diseases as for autosomal recessive, the risk at the first and second generation is considered to be zero and chromosomal diseases are assumed to be subsumed in part under autosomal dominant and X-linked diseases and in part under congenital abnormalities (Sankaranarayanan and Wassom 2008).

^boriginal unit was 'per million live births'.

Table 3. Risk of genetic diseases per Gy per 100 live births^d.

Disease class	Risk per Gy per 100 live births ^a		
	1 st generation	2 nd generation	Total
Mendelian	0.075 to 0.15	0.055 to 0.10	0.13 to 0.25
Chronic	0.025 to 0.12	0	0.025 to 0.12
Congenital abnormalities	0.20 ^b	0.040 to 0.10 ^c	0.24 to 0.30

^aThe ranges reflect biological and not statistical uncertainties.

^bEstimated from mouse data without recourse to the Doubling Dose method.

^cOn the assumption that between 20% and 50% of the abnormal progeny in the first generation may transmit the damage to the second generation (Sankaranarayanan and Wassom 2008).

^doriginal unit was 'per Gy per million progeny'.

chronic diseases, risk is assumed to be limited to the first generation (Sankaranarayanan and Wassom 2008).

In ICRP Publication 60 (ICRP 1991), equilibrium estimates were used as the basis for calculating risk coefficients for hereditary effects, and the calculation therefore took into account all generations. In 2007, the underlying assumptions supporting the equilibrium hypothesis were considered highly unrealistic and untestable and could no longer be supported (ICRP 2007). Both UNSCEAR 2001 and NAS/NRC 2006 arrived at a similar assessment regarding this issue. Therefore, for practical radiological protection purposes, the Commission recommended a genetic risk estimate based on risks up to the second generation (ICRP 2007).

Based on the results of Table 3, Table 4 presents the average risk per Gy per 100 live births estimated for the reproductive population, and the risk estimate derived for the general population (based on Table 4 in Sankaranarayanan and Wassom 2008). The risk per Gy for the whole population was taken as 40% of that of the reproductive population (0 to 30 years). The risk of genetic diseases for the whole population was then estimated to be 0.22 per Gy per 100 live births.

Calculation of nominal risk and detriment associated to hereditary effects, and derivation of the tissue weighting factor for gonads (w_T)

Integration of hereditary effects in the nominal risk

In ICRP Publication 103 (ICRP 2007), the 'heritable' nominal risk is directly derived from the estimated risk of hereditary effects estimated by UNSCEAR (UNSCEAR 2001). It is based on a genetic risk estimate up to the second

Table 4. Risk of genetic diseases per Gy per 100 live births^a.

Disease class	Reproductive population		Whole population Average risk per Gy
	Range of risk per Gy	Average risk per Gy	
Mendelian	0.13 to 0.25	0.19	0.08
Chronic	0.03 to 0.12	0.08	0.03
Congenital abnormalities	0.24 to 0.30	0.27	0.11
Total		0.54	0.22

Based on (Sankaranarayanan and Wassom 2008).

^aoriginal unit was 'per Gy per hundred progeny'.

generation. Whereas in the UNSCEAR report, risk of hereditary effect was expressed as the number of cases per 100 live births (or progeny), the nominal hereditary risk was expressed as the number of cases per 100 individuals. The tissue of relevance was identified as gonads. The same risk estimate applied to both males and females.

The estimated risk of hereditary effects was handled on the same footing as the risks of cancer to form a set of nominal risk coefficients. In this way, the nominal risk of hereditary effects was included in the global nominal risk, in addition to the other 13 components corresponding to cancer risk for specific organs or categories of organs. Nevertheless, while there is compelling evidence that radiation induces genetic effects in experimental animals, there is a lack of direct evidence of radiation-related hereditary disease in humans at any dose. Therefore, the nature of the risk and the method of calculation used for hereditary effects is completely different from the approach used for cancers. Whereas the nominal risks for cancer are based on lifetime risk estimates, based on the use of risk models derived from epidemiological studies, considering the modifying effects of age and sex, and on baseline cancer rates from different human populations (see Publication 152 for details, ICRP 2022), the nominal risk of hereditary effects is derived from a DD estimate derived from animal data.

In the whole population, the nominal risk of hereditary effects associated with gonadal dose was estimated to be around 20 cases of hereditary diseases per 10,000 persons per Gy to gonads. In the working age population, similarly to the procedure used for cancers, the nominal risk of hereditary effects was estimated to be 60% of that for the general population, leading to an estimated nominal risk of 12 per 10,000 persons per Gy for hereditary effects. The nominal risk of hereditary effects finally represents about 1.2% of the total nominal risk (ICRP 2007, Table A.4.1).

Integration of hereditary effects in the detriment

To calculate detriment from nominal risk, the same procedure as that used for cancer has been applied to the nominal risk of hereditary effects, that is weighting by three parameters reflecting lethality, quality of life and years of life lost (see Publication 152 for details, ICRP 2022). For hereditary effects, weighting values were 0.8 for lethality, 0.82 for quality of life and 1.32 for relative duration of life lost, but no information about how these values were derived is available in Publication 103 (ICRP 2007).

Using these weights, the detriment calculated for hereditary effects is 25.4 cases per 10,000 persons per Sv in the whole population. In the working age population, the detriment for hereditary effects is 15.3 cases per 10,000 persons per Sv. Finally, the detriment calculated for hereditary effects contributes about 4.4% to the total radiation detriment (ICRP 2007, Table A.4.1).

Derivation of the tissue weighting factor (w_T) for gonads

Tissue weighting factors (w_T) are used for the calculation of effective dose (ICRP 2007). These factors are determined on the basis of the relative radiation detriments for the whole population, which are the normalized radiation detriments of respective organs/tissues so that they sum to unity. A w_T value is estimated for each organ/tissue. Because of uncertainties associated with their estimation, they were grouped into four categories broadly reflecting the relative detriments. One single set of w_T is derived and applied to both sexes and all ages (ICRP 2022).

The w_T derived for the gonads in ICRP Publication 103 is 0.08 (ICRP 2007). Note that w_T for the gonads includes both hereditary effects (for which relative contribution to total detriment was 4.4%) and a component for ovarian cancers (for which relative contribution to total detriment was 1.7%) in the exposed individual. The w_T derived for the gonads decreased significantly compared to the value of 0.20 that was recommended in ICRP Publication 60 (ICRP 1991).

Discussion

This article presents a comprehensive review of the methodological framework used to estimate the hereditary risks of radiation exposure. Especially, it describes and discusses the concept of the DD as well as changes over time in its conceptual basis and calculation methods and in its application in the radiological protection system.

Concept and calculation of the risk of hereditary effects and evolution over time

The concept of the DD refers to the amount of the radiation dose required to double the number of spontaneous genetic mutations in a given population of cells. It is calculated as a ratio of the average rate of spontaneous and induced mutations at a set of defined gene loci. The conceptual bases and database used to calculate DD have undergone various changes and fluctuations over time. For instance, two correction factors, the MC and PRCF, were introduced to consider the fact that not all mutations lead to a disease and that the specific locus mutations used to evaluate the DD in mice are not indicative for the entire spectrum of inducible hereditary diseases in humans.

Transfer of risk from mice to humans

Despite the evolutions that have occurred in the conceptual basis of DD over time, various uncertainties persist, which

are bridged by assumptions and extrapolations. One such assumption is that the mutation rates induced by radiation exposure in humans can be deduced from that in mice. This assumption was unavoidable due to the absence of reliable evidence of radiation-related hereditary effects observed in human populations. Although the assumption was considered biologically plausible in the years ~ 2000 (Sankaranarayanan and Chakraborty 2000a, 2000b), it has been called into question recently (Nakamura et al. 2023). Also, differences may exist between humans and rodents in the spectrum between spontaneous mutations and radiation-induced mutations.

Since 2001, the calculation of DD is based on spontaneous mutation rates from human populations, which is significant improvement compared to previous estimates which were based on mice data for both the induced mutation rates and the spontaneous mutation rates (UNSCEAR 2001). In the chemical field, uncertainty factors (also known as safety factors or protection factors) are often incorporated into risk assessments to reflect existing scientific uncertainty about transposition from one species and individual to another. These factors are applied to toxicity data to establish a protective margin in the definition of the dose that should not produce an effect in the human population (ANSES 2017). However, although the calculation of the genetic disease risk for radiation is still based on animal data, no 'uncertainty factor' is applied for the transfer of this risk to humans. Instead, a very low PRCF is applied to reflect the differences between the rates of induced mutations in mice and those of potentially recoverable induced mutations in humans. Although these PRCF values are derived from scientific observations, it is not clear that the overall process of estimating hereditary risk in humans can be considered conservative or prudent today.

In order to estimate the risk of hereditary effects resulting from exposure to ionizing radiation in the human population, mouse data on induced mutations must be used due to the absence of corresponding human data on radiation-induced germ cell mutations (Sankaranarayanan and Chakraborty 2000a, 2000b). It is worth noting that most of the available mouse data concerning radiation-related hereditary effects have been derived from studies involving moderate to high doses of low-LET X- or γ -irradiation, while the risk assessments have been made for low-LET, low dose/chronic radiation exposures assuming that chronic gamma radiation is significantly less effective than acute X-radiation in inducing specific locus mutations in spermatogonia (Russel 1958). Specifically, the suggestion has been made to apply a dose-rate reduction factor of 3 for extrapolating to the effects of chronic radiation and making them applicable to human irradiation conditions (Sankaranarayanan and Chakraborty 2000a, 2000b). The validity of such an assumption of a reduction of hereditary risks at low dose-rates has not been updated for more than 60 years.

In addition, it should be considered that the types of abnormalities and their effects on the individual are different in mice and humans, that the average rate of induced mutations was calculated for 34 genetic loci in mice and may be

an overestimate (the rate at which induced disease-causing mutations are seen in human live births following parental radiation exposures may be much lower than that of induced mutations in mice (NAS/NRC 2006)), and that data from female mice have not been used. Despite of these shortcomings, risk estimates for humans will have to rely on the above assumptions until more information becomes available (Sankaranarayanan and Chakraborty 2000a, 2000b; UNSCEAR 2001).

Number of generations considered

In 2007, the estimation of the hereditary risks was limited to the first and second generations of an irradiated population, whereas before the genetic risk was calculated for up to 10 generations (ICRP 1991, 2007). This change was justified by the fact that underlying assumptions supporting the equilibrium hypothesis over many generations were considered highly unrealistic and untestable and could no longer be supported (UNSCEAR 2001; NAS/NRC 2006; ICRP 2007). Even if the impact of such change was estimated to be limited (Sankaranarayanan and Wassom 2008), this change remains controversial today and would merit a better explanation.

Categories of diseases considered

The categories of hereditary effects considered in the calculation of the hereditary detriment include Mendelian diseases, chromosomal diseases, and multifactorial diseases including both congenital abnormalities and chronic diseases. Nevertheless, these categories are not necessarily mutually exclusive. For example, a small proportion of congenital abnormalities such as cleft lip shows Mendelian transmission. Also, the fact that one individual can have several chronic diseases is not considered in the estimation of P, which may lead to an overestimation of the number of affected individuals.

Some of the hereditary effects considered as stochastic effects are also considered as tissue reactions in other parts of the radiological protection system. This is the case for example for congenital malformations, that are considered as stochastic effects when inherited from parents exposed before conception, but as tissue reactions when due to exposure during pregnancy. Also, coronary heart diseases are considered as stochastic effects in offspring but as tissue reactions in exposed parents. The explanation for these apparent discrepancies is that the classification of the radiation effects is based not on the symptom, but on the pathogenic mechanism.

Aspects related to the possibility that mutations may cause predisposition to cancers were reviewed by UNSCEAR. Collectively, such cancer-predisposing mutations were believed to account for about 1% of cancer cases. Finally, it was estimated that the increase in cancer risks in a heterogeneous population was small (UNSCEAR 2001). Nevertheless, today, the genetic component in the determination of cancer is well recognized (Pomerantz and Freedman 2011), and between 5 and 10% of cancers are considered to

be linked to an inherited genetic mutation (NCI 2023). This applies for instance to breast, ovary or colon cancers. The non-inclusion of cancers in the list of hereditary effects may be reviewed in the light of recent scientific knowledge.

Some outcomes, such as stillbirth or changes in the sex-ratio are often considered in epidemiological studies as indicators of potential hereditary effects. Today, these effects are not considered as hereditary effects of radiation exposure and are not considered in the calculation of the hereditary risk in the radiological protection system.

Source of information on human baseline rates of genetic diseases

The data used to determine the baseline disease frequency P used in the calculation of genetic risks have not been updated for many years. For Mendelian diseases, the sources are from the 1970s (Trimble and Doughty 1974; UNSCEAR 1977), and for congenital diseases and chronic diseases they are from the 1980s (Czeizel and Sankaranarayanan 1984; Czeizel et al. 1988). Furthermore, the data were sometimes derived from a specific population: British Columbia Survey for chromosomal diseases (Trimble and Doughty 1974) or Hungarian population for congenital diseases or chronic diseases (Czeizel and Sankaranarayanan 1984, Czeizel et al. 1988). These data do not reflect potential evolutions in the classification of genetic diseases in recent years, or potential variations between groups of populations. The identification of more recent data sources, more representative of current knowledge on genetic diseases, and more representative of the general population would be advisable.

Studies of hereditary effects of radiation exposure in human populations

The largest cohort where potential hereditary effects in the children of radiation-exposed parents can be investigated include more than 70,000 children of exposed A-bomb survivors (Ozasa et al. 2018). A range of potential genetic effects was studied such as untoward pregnancy outcomes, congenital malformations, chromosomal aberrations, sex ratio and many others. Although associations of some of the endpoints with parent exposure was found, the overall result was not significant. This ‘negative’ finding may be due to the relatively low conjoint dose (in the order of 10 mGy) and the choice of health endpoints.

The issue of genetic harm from parental radiation exposure became prominent again, when in 1990 the results of a case-control study suggested that paternal preconceptional irradiation of workers at the Sellafield nuclear installation in north-west England increased the risk of childhood leukemia and that this could explain a ‘cluster’ of cases of leukemia in children living in the nearby village of Seascale (Gardner et al. 1990). This observation motivated other studies that did not provide supporting evidence (Doll et al. 1994; Wakeford 2003; 2013) and the above-mentioned hypothesis has effectively been abandoned (COMARE 2016).

One group of radiation-exposed people was identified of potentially providing sound evidence for the level of risk of hereditary diseases following radiation exposure of parents: ‘Studies of the offspring of childhood cancer survivors offer the unique opportunity to evaluate whether preconception radiation therapy can result in hereditary genetic effects. ... Such studies should provide additional evidence whether current estimates of radiation-related hereditary effects in humans are reasonable.’ (Boice et al. 2003). However, up to now these studies do not demonstrate any radiation-related hereditary effects (Boice 2020). Currently a large Study of Genetic Consequences of Cancer Treatment includes about 15,000 survivors of childhood and young adult cancer. In their offspring, the rates of clinical genetic disease will be evaluated (Barton 2012).

The design of studies on diseases or disorders with clinical relevance and known bases in human genetics evidence appears today of utmost importance to provide reliable evidence in future estimates of human radiation-related genetic risk.

Also, well-designed trio studies (analyses of family trio sequencing, searching for differences in DNA between the parents exposed to radiation and their children) may provide informative results in the coming years (Yeager et al. 2021; Amrenova et al. 2023). In recent years, new technologies and approaches in testing for radiation effects have been developed, results from epidemiology studies have become available, and mechanisms of disease development on gene, DNA and protein levels have been discovered. One such mechanism is epigenetics, which refers to changes in gene expression that takes place without a change in the DNA sequence. Therefore, all this would be worth taking into account when calculating genetic risk.

Inclusion of hereditary effects in the calculation of nominal risk and detriment

As hereditary effects are considered as stochastic effects, they have been included in the calculation of the detriment, which is intended to integrate all stochastic effects of radiation exposure into one single risk indicator (ICRP 2022). This has been the case since the introduction of the concept of detriment in the radiological protection system by ICRP in the 1970s (ICRP 1977).

Nevertheless, the way hereditary effects are integrated in the calculation of nominal risks, in the calculation of radiation detriments and finally in the construction of the effective dose is not straightforward. Some assumptions or methodological choices raise questions, such as the change in units between the expression of genetic risk (in number of cases per 100 live births or progeny) to hereditary risk (in number of cases per 100 individuals), or the justification to use severity weights that were initially derived for cancers.

The inclusion of hereditary risk as an add-in in the global nominal risk masks the large differences in the level of knowledge and in the magnitude of uncertainties between hereditary effects and cancer risks. Also, the difference in the nature of the risk between cancers (lifetime risk of

cancer in exposed individuals) and hereditary effects (congenital malformations and non-cancer chronic diseases in the descendants of exposed individuals) is not well reflected in the current calculational scheme. The justification of including both in one single indicator of detriment, and consequently in the construction of the effective dose, may be debatable.

Traceability and clarity

In its recent Publication 152, ICRP clearly highlighted the need to improve transparency and comprehensibility in the calculation and expression of the radiation detriment in its next recommendations. Main elements raised were ensuring the traceability of the calculation, identifying major sources of uncertainty and quantifying their impact, and improving interpretability of the results (ICRP 2022). This clearly applies to hereditary effects.

A first point of clarification may be in the terminology of the effects. The interchangeable use of 'genetic effects' or 'hereditary effects' or 'heritable effects' has to be clarified or simplified. Also, the units have to be homogenized (cases per progeny vs cases per person).

Conclusion

This article highlights the complexity of the calculational method used to quantify the risk associated with hereditary effects, and the diversity of input data and assumptions used overall in the different steps of the calculation process. This process would benefit from clarification and a better explanation. This includes the identification of data sources, a clear description of what health endpoints are included and justification of why some others are not included, and a clarification of the different steps of the calculation process (not only for the quantification of genetic risks, but also for the assessment of nominal risk and detriment). Also, an effort should be dedicated to the identification (and where possible, quantification) of uncertainties, and discrimination of what is 'science-based', and what is 'expert judgment'.

Specific attention may also be given to communication aspects. Today, the possibility of radiation-related deleterious effects in offspring and next generations is still a major source of fear for the general public, and a major concern for parents exposed to ionizing radiation from occupational, medical or environmental sources. The meaning and magnitude of the detriment associated with hereditary effects could be better explained, especially regarding the justification to include it in the detriment even if no effect has been consistently demonstrated among humans up to now.

Disclosure statement

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

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




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