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Objectives and achievements of the HUMN project on its 26th anniversary

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Abbreviations: BN, binucleated cell; BUCMN assay, Buccal Cell Micronucleus Assay; CBMN assay, Cytokinesis-Block micronucleus assay; CBMNcyt assay, Cytokinesis-Block MN cytome assay; FR, frequency ratio; HUMN project, Human Micronucleus project; MR, mean ratio; MN, micronucleus or micronuclei; MNi, micronuclei; MNed, micronucleated i.e. cells containing MN; MONO, mononucleated cell; NBUDS, nuclear buds; NPBs, nucleoplasmic bridges; PBL, peripheral blood lymphocytes; RBCs, red blood cells; RR, relative risk; ZIP, Zero Inflated Poisson.

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ABSTRACT

Micronuclei (MN) are a nuclear abnormality that occurs when chromosome fragments or whole chromosomes are not properly segregated during mitosis and consequently are excluded from the main nuclei and wrapped within nuclear membrane to form small nuclei. This maldistribution of genetic material leads to abnormal cellular genomes which may increase risk of developmental defects, cancers, and accelerated aging. Despite the potential importance of MN as biomarkers of genotoxicity, very little was known about the optimal way to measure MN in humans, the normal ranges of values of MN in healthy humans and the prospective association of MN with developmental and degenerative diseases prior to the 1980's. In the early 1980's two important methods to measure MN in humans were developed namely, the cytokinesis-block MN (CBMN) assay using peripheral blood lymphocytes and the Buccal MN assay that measures MN in epithelial cells from the oral mucosa. These discoveries greatly increased interest to use MN assays in human studies. In 1997 the Human Micronucleus (HUMN) project was founded to initiate an international collaboration to (i) harmonise and standardise the techniques used to perform the lymphocyte CBMN assay and the Buccal MN assay; (ii) establish and collate databases of MN frequency in human populations world-wide which also captured demographic, lifestyle and environmental genotoxin exposure data and (iii) use these data to identify the most important variables affecting MN frequency and to also determine whether MN predict disease risk. In this paper we briefly describe the achievements of the HUMN project during the period from the date of its foundation on 9th September 1997 until its 26th Anniversary in 2023, which included more than 200 publications and 23 workshops world-wide.

1. Background and early history of MN assays

The fields of mutagenesis and carcinogenesis research in eukaryotic cells emerged from the early observations that certain chemicals and ionising radiation can induce chromosomal aberrations [1,2] and that cancer cells often exhibit a wide range of structural and numerical chromosomal abnormalities [3,4].

Micronuclei (MN) were reported in erythrocytes by Howell and Jolly decades before metaphase analysis of chromosome aberrations became established [5,6]. For this reason, it was not known at that time that MN in erythrocytes originated from chromosome fragments or whole chromosomes that were not segregated properly to the daughter nuclei of their normoblast precursors during mitosis [7].

The first papers to report that MN were induced by chemical genotoxins and ionising radiation in rodent bone-marrow cells and peripheral blood erythrocytes and the adoption of this methodology for routine in vivo genotoxicity testing in rodents were reviewed comprehensively in a 1983 report by the U.S. Environmental Protection Agency Gene-Tox Program [8]. In humans, increased MN were first reported in peripheral blood lymphocytes and/or erythrocytes in subjects with folate and/or vitamin B12 deficiency, exposure to ionising radiation and treatment with cytotoxic drugs [8–12].

The use of peripheral blood lymphocytes is of great interest because they can be easily cultured and used to study the effects of various biological, chemical, radiological, nutritional and genetic factors on chromosome aberrations and MN formation *in vivo*, *ex vivo* and in *vitro*. The use of erythrocyte and lymphocyte MN assays in humans gradually increased; and MN assays in cells from easily accessible epithelial tissues, such as buccal, nasal, cervical and urothelial cells started to be developed which enabled the possibility to compare MN frequencies

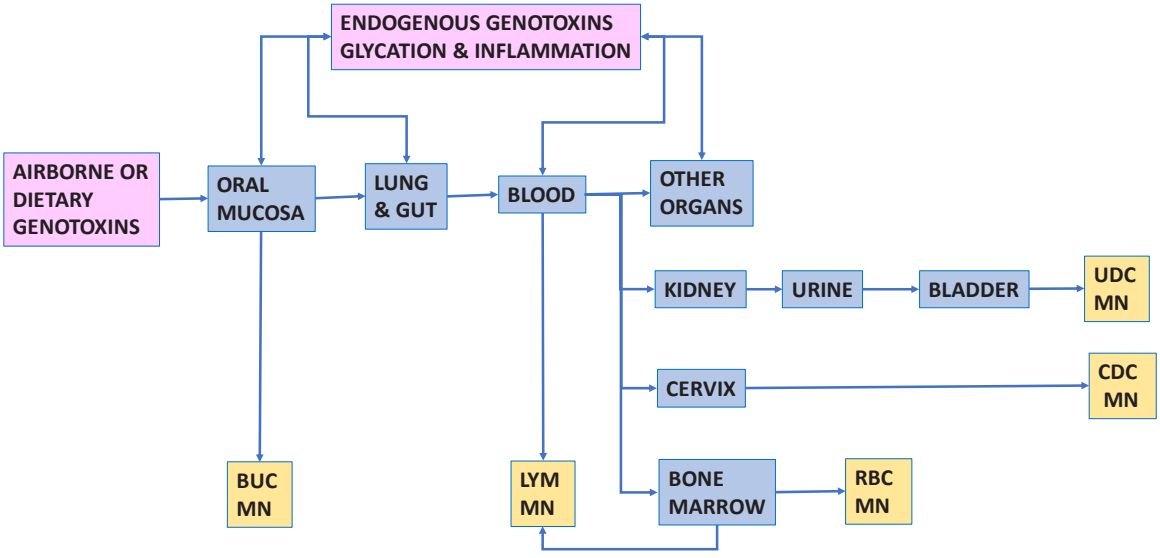

Fig. 1. Flow diagram of inter-relationship between endogenous/exogenous genotoxin, glycation and inflammation exposure and their sequential impact on micronucleus (MN) formation in tissues for which MN assays have been established (BUC MN, micronuclei in buccal cells; CDC MN, micronuclei in cervix derived cells; LYMN MN, micronuclei in lymphocytes; RBC MN, red blood cell micronuclei; UDC MN, micronuclei in urine derived cells). Other factors not shown in the diagram that influence MN formation include genetic susceptibility to genotoxin-induced micronuclei and the aggravating effect of deficiency in certain micronutrients (e.g. folate, vitamin B-12 and zinc deficiency) that are required for DNA replication and repair and are known to increase MN formation when their supply is inadequate. Reproduced with permission from Elsevier from: Fig. 4 in Fenech M, Knasmueller S, Knudsen LE, Kirsch-Volders M, Deo P, Franzke B, Stopper H, Andreassi MG, Bolognesi C, Dhillon VS, Laffon B, Wagner KH, Bonassi S. "Micronuclei and Disease" special issue: Aims, scope, and synthesis of outcomes. Mutat Res Rev Mutat Res. 2021 Jul-Dec;788:108384. doi: 10.1016/j.mrrev.2021.108384. Epub 2021 Jun 5. PMID: 34893149.

across multiple tissues. Fig. 1 illustrates the types of cells that can be used practically in human studies and their relationship with each other and exposure to genotoxins.

The wide-spread use of lymphocyte culture for metaphase analysis of chromosomes made it practical for laboratories to use this technology to also measure MN in lymphocytes. However, the accuracy of this approach was constrained by the large variability of MN frequencies which depended on the proportion of cells completing one nuclear division after exposure to a genotoxic insult. MN are mainly expressed in dividing cells during telophase in mitosis when lagging chromosomes or chromosome fragments are enveloped by membrane independent of the main daughter nuclei [Fig. 2]. It became evident that a method which clearly distinguished between non-divided cells and cells that completed one nuclear division was required so that MN could be scored specifically in once-divided cells and thus prevent inaccurate MN measurement caused by differences in cell division kinetics [13–15]. Several approaches were reported to achieve this, but the most efficient and reproducible method was proven to be the cytokinesis-block method developed by Fenech and Morley [13–15]. In this method cells in mitosis are blocked in the binucleated stage in telophase [Fig. 3A] by using cytochalasin-B, a fungal metabolite shown to inhibit the formation of the microfilament ring which is essential for cytokinesis [16,17]. This method, known as the cytokinesis-block micronucleus (CBMN) assay, was rapidly adopted by several laboratories world-wide making it practical to consider the possibility of international collaboration to address some important questions on the use of this assay as a biomarker of exposure to genotoxins and its biological significance in health and disease which are discussed below.

2. Founding of the HUMN project

Early studies showed that lymphocyte MN frequency measured using the CBMN assay was positively correlated with age and exposure to low dose X-rays, and higher in females relative to males, however, these results were restricted to a single laboratory in the early 1980's [18–20]. Furthermore, at that time, although MN were reported to be increased in rodents exposed to genotoxic carcinogens *in vivo* [8] there were few in vivo studies in humans exposed to chemical genotoxins and some of these were done using methods that were not yet validated in laboratory inter-comparison studies or used cell types other than lymphocytes or performed the lymphocyte MN assay without using the cytokinesis-block technique [21–24]. In addition, there was a growing interest in determining whether cytogenetic biomarkers of DNA damage or genotoxic effect could predict risk of cancer and other age-related diseases in humans [25,26]. During this period, it also became increasingly evident that the CBMN assay could also be an effective tool for measuring chromosome malsegregation events and aneuploid nuclei if pan-centromeric or chromosome-specific probes were used to identify the distribution of chromosomes among the main nuclei and micronuclei in binucleated cells [27–30] [Figs. 2,3]. This widespread interest in the lymphocyte CBMN assay was also reflected by development of promising approaches to automate the technique using image cytometry [31,32].

A chromosome segregation and aneuploidy conference in April 1995 in Sorrento, Italy, organised by Angelo Abbondandolo and Baldev Vig [33], provided the spark for the initiation of the HUMN project when Michael Fenech enquired whether Angelo knew an epidemiologist who might be interested in working on an international project to address important questions relating to the effect of methodological, demographic, lifestyle and environmental exposure variables affecting MN frequency and prospective association of this biomarker, measured using the lymphocyte CBMN assay, with cancer. Angelo suggested contacting Stefano Bonassi who enthusiastically accepted to join Michael in exploring this initiative. After more than one year of exchanging emails and numerous discussions Stefano and Michael agreed to call this project the Human Micronucleus (HUMN) Project to emphasise the focus on human studies.

The official founding of the HUMN project occurred at the 7th International Conference on Environmental Mutagenesis occurred in Toulouse, France, on 9th September 1997 at a workshop titled "*Meeting on the International Collaborative Project on Micronucleus Frequency in Human Populations*" [http://www.iaemgs.org/Historical.asp]. The first HUMN project coordinating group consisted of Stefano Bonassi, Nina Holland, Errol Zeiger, Peter Chang and Michael Fenech bringing together expertise in epidemiology, MN assay using buccal epithelial cells, genotoxicity testing, human studies using the lymphocyte CBMN assay, and the biology of biomarkers scored in the lymphocyte CBMN assay.

The coordinating group determined that the initial goal should be a "manifesto" that explained the purpose of the HUMN project. It was

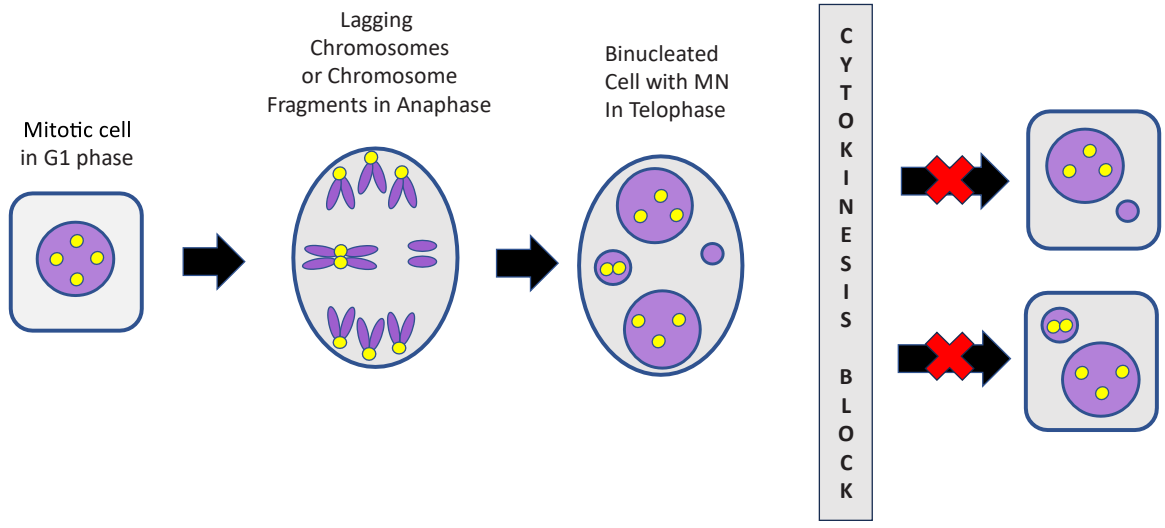

Fig. 2. Formation of micronuclei from lagging whole chromosomes or acentric chromosome fragments during anaphase and their presence in binucleated cells following cytokinesis blockade with cytochalasin-B in telophase. Centromeres are indicated by small yellow dots on chromosomes, micronuclei and on nuclei. Reproduced and adapted with permission from Elsevier from: Fig. 1 in Fenech M, Knasmueller S, Bolognesi C, Holland N, Bonassi S, Kirsch-Volders M. Micronuclei as biomarkers of DNA damage, aneuploidy, inducers of chromosomal hypermutation and as sources of pro-inflammatory DNA in humans. Mutat Res Rev Mutat Res. 2020 Oct-Dec;786:108342. doi: 10.1016/j.mrrev.2020.108342. Epub 2020 Oct 28. PMID: 33339572.

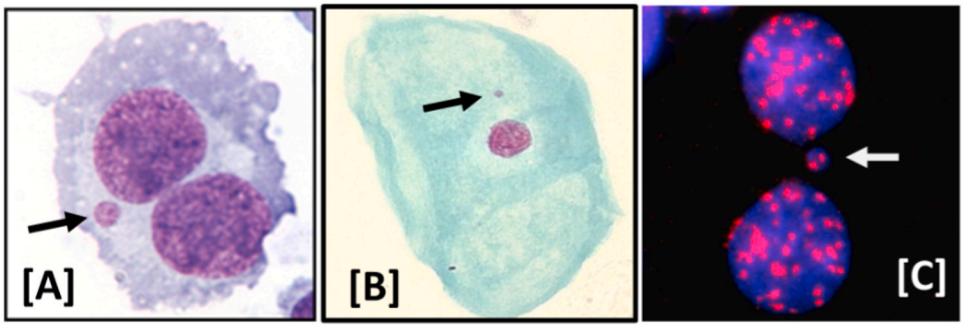

Fig. 3. Photomicrographs of cells with micronuclei. [A] Cytokinesis-blocked binucleated lymphocyte with one micronucleus stained using Wright-Giemsa stain. [B] Buccal cell with one micronucleus stained with Feulgen and Light green. [C] Cytokinesis-blocked binucleated lymphocyte stained with DAPI containing one micronucleus that is centromere positive. DAPI staining and centromere probe staining are visualised using fluorescence microscopy. Photomicrograph [A] is reproduced with permission from Nature Publishing Group from: Fig. 3f in Fenech M. Cytokinesis-block micronucleus cytome assay. Nat Protoc. 2007;2 (5):1084–104. doi: 10.1038/nprot.2007.77. PMID: 17546000. Photomicrograph [B] is reproduced with permission from Elsevier from: from Figure 12 A in Bolognesi C, Knasmueller S, Nersesyan A, Thomas P, Fenech M. The HUMNxl scoring criteria for different cell types and nuclear anomalies in the buccal micronucleus cytome assay - an update and expanded photogallery. Mutat Res. 2013 Oct-Dec;753(2):100–113. doi: 10.1016/j.mrrev.2013.07.002. Epub 2013 Aug 11. PMID: 23942275. Photomicrograph [C] is reproduced with permission from Elsevier from: Fig. 2B in Vral A, Fenech M, Thierens H. The micronucleus assay as a biological dosimeter of in vivo ionising radiation exposure. Mutagenesis. 2011 Jan;26(1):11–7. doi: 10.1093/mutage/geq078. PMID: 21164177.

agreed that a key objective of the HUMN project was to collect data on MN frequencies in different human populations using assays that are already widely used such as the lymphocyte CBMN assay and the Buccal MN assay [Figs. 3A and 3B].

Furthermore, data should then be used to:

(1) determine the extent of variation of 'normal' MN values between laboratories and identify the dominant factors affecting baseline MN frequency,

(2) provide information on effect of assay protocol modifications on MN scoring,

(3) design and test improved MN assay protocols for use with different types of human cells,

(4) determine if MN frequency is a valid biomarker of ageing and diseases such as cancer.

This manifesto was published in 1999 [34], two years after the official foundation of the HUMN project. The achievements of the HUMN project from its foundation in 1997 until 2023 have been published in peer-reviewed journals and are described briefly below. These achievements together with further details are presented in a more precise chronological order in Supplementary Table 1.

3. Achievements of the HUMN project with respect to the lymphocyte CBMN assay

During the initial period of 1997–2001 some notable achievements and advances were already emerging from the HUMN project group. 1997 was particularly important because a study published in Lancet showed for the first time that the lymphocyte CBMN assay can be used successfully to measure increases in chromosomal damage in people exposed to chronic low-dose, low-dose-rate gamma-radiation due to contamination of steel rods with cobalt 60 used to build their apartments [35]. Another study on children exposed to the Chernobyl catastrophe

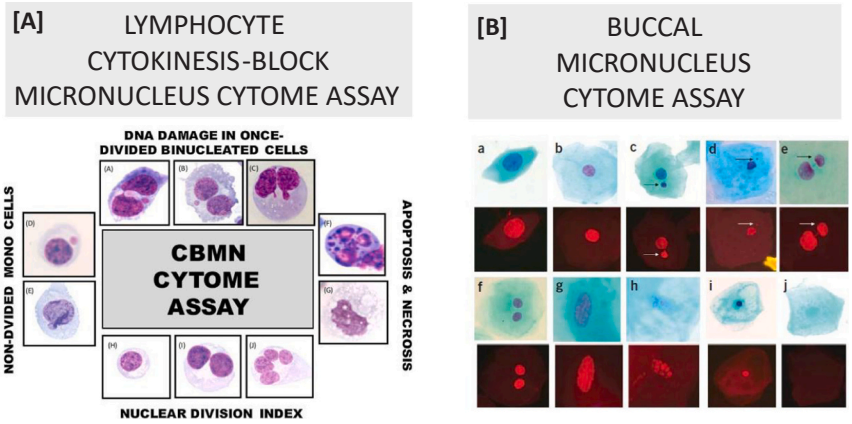

Fig. 4. [A] Biomarkers and different cell types in the Lymphocyte Cytokinesis-Block Micronucleus Cytome Assay stained using Wright-Giemsa stain and viewed by transmitted light. {A} Binucleated (BN) cell with micronucleus (MN) and nucleoplasmic bridge (NPB); {B} BN cell with MN; BN cell with Nuclear buds (NBUD); {D} Mono-nuclear (MONO) cell with MN; {E} MONO cell with NBUD; {F} Apoptotic cell; {G} Necrotic cell; {H} MONO cell; {I} BN cell}; {J} Multinucleated cell. Photomicrographs in Fig. 4 [A] are reproduced with permission from Nature Publishing Group from: Fig. 3 in Fenech M. Cytokinesis-block micronucleus cytome assay. Nat Protoc. 2007;2(5):1084–104. doi: 10.1038/nprot.2007.77. PMID: 17546000. Fig. 4 [B] Biomarkers and different cell types in the Buccal Micronucleus Cytome Assay stained using Feulgen and Light Green and viewed by transmitted light or fluorescence with a far-red filter; (a) basal cell; (b) differentiated cell; (c) early differentiated cell with micronucleus (arrow); (d) late differentiated cell with micronucleus (arrow); (e) differentiated cell with nuclear bud (arrow); (f) binucleated cell; (g) condensed chromatin cell; (h) karyorrhectic cell; (i) pyknotic cell; (j) karyolytic cell. Upper panels light microscopy, lower panels fluorescence microscopy. Photomicrographs in Fig. 4 [B] are reproduced with permission from Nature Publishing Group from: Fig. 5 in Thomas P, Holland N, Bolognesi C, Kirsch-Volders M, Bonassi S, Zeiger E, Knasmueller S, Fenech M. Buccal micronucleus cytome assay. Nat Protoc. 2009;4(6):825–37. doi: 10.1038/nprot.2009.53. Epub 2009 May 7. PMID: 19444240.

showed that the lymphocyte CBMN assay could detect the genotoxic effects of radionuclide contamination and that the increase in MN frequency was discernible both in mononucleated and binucleated cells [36]. Subsequently, a proposal was made that inclusion of MN in non-divided mononuclear lymphocytes and necrosis/apoptosis may provide a more comprehensive CBMN assay for biomonitoring purposes which led to the concept of the CBMN "cytome" (CBMNcyt) assay [37–39] and subsequently measurement of chromosome loss, chromosome non-disjunction, nuclear buds and nucleoplasmic bridges were also added to the cytome concept [Fig. 4 A] [40,41].

By 2000, data from nearly 700 subjects were contributed by 25 laboratories from 16 countries. Differences were evident in methods used such as type of culture medium, concentration of cytochalasin-B, amount of foetal calf serum in culture medium, and in culture method used (isolated lymphocytes or whole blood cultures). Differences in MN scoring criteria were also apparent. Overall median MN frequency (and interquartile range) in nonexposed subjects was 6.5 (3−12) per 1000 binucleated (BN) cells. Age-related increase in MN frequency was evident in almost all laboratories. Effect of sex was also present, with females having 19 % (95 % CI: 14–24 %) higher level of MN incidence relative to males. Random-effects statistical models for correlated data, which included exposure to genotoxic factors, host factors, methods, and scoring criteria, explained 75 % of the total variance, with the largest contribution attributable to laboratory methods. These first results from the pooled data from laboratories using the lymphocyte CBMN assay were published in 2001 [42].

Because methodological parameters such as criteria for identifying BN cells and scoring MN within them accounted for 47 % of the variability in micronucleated (MNed) cell frequency it was decided to perform an inter-laboratory slide scoring study and to establish and publish a set of detailed scoring criteria for the lymphocyte CBMN cytome assay. Thirty-four laboratories participated in the scoring exercise and all of them correctly ranked micronucleated (MNed) BN cell frequency in cells exposed to different gamma ray doses (0 Gy, 1 Gy, 2 Gy) [43].

The detailed description of the scoring criteria together with multiple photomicrographs for (i) classifying mononucleated, binucleated and multinucleated, as well as necrotic and apoptotic cells and (ii) identifying and distinguishing between MN, nucleoplasmic bridges (NPBs) and nuclear buds (NBUDS) within binucleated cells or MN and NBUDS in mononucleated cells in the CBMN cytome assay using isolated lymphocyte cultures was provided to all study participants and subsequently published [44].

A few years later a detailed protocol for the cytokinesis-block micronucleus cytome assay in peripheral blood lymphocytes was published in Nature Protocols [41]. This protocol together with the scoring criteria manuscript provide the most detailed and comprehensive description of how to conduct the lymphocyte CBMN cytome assay [41, 44].

Using the accumulated data from 5710 persons, the HUMN project investigated the relationship between MN frequency and smoking [45]. The results showed a U-shaped curve with significant MN increases in those smoking more than 30 cigarettes per day.

Another important variable that might affect MN frequency in lymphocytes is nutritional deficiency but evidence for this prior to or in 1997 was mainly limited to studies relating to folate and/or vitamin B12 deficiency [46–49]. The first study of the HUMN project addressing the effect of malnutrition across multiple micronutrients was published in 2005 [50]. The study reported that low dietary intake of calcium, folate, nicotinic acid, vitamin E, retinol, beta-carotene and high intake of pantothenic acid, biotin and riboflavin are significantly associated with increased lymphocyte MN frequency.

Several other similar studies were reported in later years indicating the suitability of the lymphocyte CBMN assay to measure the genotoxic effects of micronutrient deficiency or excess [51–55]. In addition, several papers were published consequently to test whether supplementation with micronutrients or intervention by dietary pattern change altered MN frequency [56].

From the 1990's onwards there was an increased interest on whether MN frequency in lymphocytes is affected by common polymorphisms in genes coding for enzymes involved in carcinogen metabolism, antioxidant defense, B vitamin metabolism and DNA repair enzymes. The first paper on this topic was published by Carstensen et al. in 1993[57], and in 2006 a comprehensive systematic review was published on the effects of *GSTM1* and *GSTT1* polymorphisms on MN frequencies in human lymphocytes [58]. Another systematic review in 2008 investigated and reported on the effects of carriage of the *hOGG1*(326), *XRCC1*(399) and *XRCC3*(241) polymorphisms on MN frequencies in human lymphocytes in vivo [59]. This was followed by further numerous studies that also explored the interactive effects of enzymes involved in micronutrient metabolism such as the common *C677T* polymorphism in the *MTHFR* gene and the *M*TR (G80A) polymorphism both required for folate metabolism [60–79].

One of the major achievements of the HUMN project was to complete for the first time a prospective epidemiological study of 6718 subjects from of 10 countries, linking base-line lymphocyte MN with cancer incidence data. This study revealed that an increased MN frequency in peripheral blood lymphocytes predicts the risk of cancer in humans [80]. All cancer incidence was increased for subjects in the groups with medium (RR=1.84) and high MN frequency (RR=1.53). The same groups also showed a decreased cancer-free survival. The results from this study provided the initial evidence that MN frequency in peripheral blood lymphocytes (PBL) is a predictive biomarker of cancer risk in healthy subjects. This seminal study of lymphocyte MN and disease risk led to other prospective studies showing that lymphocyte MN frequency measured using the CBMN assay was also predictive, in other cohorts, of cancer risk and cardiovascular disease mortality in apparently healthy subjects, adverse cardiac events in patients with coronary artery disease, and also pregnancy complications such as pre-eclampsia and/or intrauterine growth restriction in women whose MN frequency was measured in early pregnancy at 18 weeks gestation [81–85].

4. Achievements of the HUMN project with respect to the buccal micronucleus assay

The buccal cell micronucleus (BUCMN) assay [Fig. 3B], first proposed by Stich et al. [86,87], is a useful method to measure DNA damage in epithelial cells caused by environmental mutagens, adverse lifestyle habits, poor nutrition, and due to inherited defects in DNA repair. [88–92].

Following the success with the lymphocyte CBMNcyt projects, the HUMN project coordinating group put together a compelling case to harmonise and standardise the buccal MN cytome (BUCMNcyt) assay [Fig. 4B] which was published in 2007 [93–95].

The growing interest in using buccal cells led to increased diversity in the protocols used for sampling, staining of cells and for scoring MN and other nuclear anomalies [96–103]. To resolve these issues the HUMN project completed three reviews and one workshop that identified important knowledge gaps regarding the biology of MN expression in buccal cells and technological constraints of the assay that needed to be resolved. [103–106].

In the interim it was sensible to suggest that Feulgen/Fast green staining and the scoring criteria of Tolbert et al. [97] be approved as the basic method.

The HUMN project perspective, based on comprehensive review of the literature on the status and knowledge gaps of the micronucleus assay in human buccal cells as a tool for biomonitoring DNA damage was published in 2008 [105]. This report also included contributions from a workshop on the same topic held in Turkey [106]. This review covered important aspects about the current status such as (i) application in biomonitoring studies, (ii) methodology, including cell collection, staining, slide preparation and scoring criteria and (iii) study design.

With regards to important knowledge gaps the following were identified: (i) effect of cell division kinetics on MN frequency, (ii) biology of the formation of MN and other nuclear anomalies in buccal cells, (iii) demographic, lifestyle, environmental and genetic variables affecting buccal MN frequency, (iv) correlation of buccal MN frequency with MN in lymphocytes and other tissues and (v) association of buccal MN frequency with aging and chronic diseases. It was agreed at the workshop in Turkey that three activities should be given priority, namely (a) a method for collection of databases, (b) writing of a protocol based on the most commonly used and best validated procedures and (c) an inter-laboratory slide-scoring exercise in this order.

In 2009 a survey was performed on the use of the BUCMNcyt assay [107]. The survey data were collected using a questionnaire regarding the methods used to perform the assay and type of epidemiological data that were collected. In total 43 laboratories completed the questionnaire. It was estimated that data from 15,103 subjects could be available for analysis. Inter-laboratory protocol differences were common suggesting the need for method standardization. Furthermore, results of this survey also identified epidemiological variables (e.g. age, dietary habit, occupation) that affect buccal MN frequency.

A meta-analysis of 63 buccal MN studies identified the most important confounding factors which increased MN frequency i.e. age, smoking and exposure to genotoxicants [103]. The paper also reported a significant positive correlation between MN frequency in buccal cells and lymphocytes and recommended scoring 4000 cells to achieve a robust MN frequency estimate.

Further analysis of the buccal MN data provided information on base-line frequencies of MN in healthy subjects which were reduced with higher fruit intake and increased in the elderly and various genotoxin exposure and disease states; MN levels were also higher if stains that are not DNA specific are used [108].

Another major achievement was the publication of a detailed BUCMNcyt assay protocol and scoring criteria [109,110]. These methods provided the basis for an inter-laboratory slide scoring exercise amongst three experienced laboratories which revealed good agreement for scoring MN in differentiated buccal cells [111]. A second slide scoring exercise amongst 14 less experienced laboratories also reported concordance in measurement of MN in differentiated buccal cells but greater variability with scoring other cytome biomarkers [112].

Clinical application of the BUCMNcyt assay was another aspect that was systematically reviewed. It is evident that MN incidence in buccal cells is markedly elevated in oral head and neck cancer cases and other cancers generally [113]. This association with cancer needs further validation in large prospective studies.

5. Other objectives and achievements

5.1. Radiation biodosimetry

Shortly after its creation it became evident that the lymphocyte CBMN assay had strong potential to become a reliable biodosimeter of exposure to ionsing radiation not only in the high dose range 1.00–4.00 Gy) but also in the low dose range 0.05–0.50 Gy of acute or chronic ionising radiation exposure [35,114]. Because of the ease to score MN in cytokinesis-blocked binucleated cells relative to the conventional metaphase analysis of chromosome aberrations, the CBMN assay was adopted by numerous radiation biodosimetry laboratories and, also, used to identify radiation sensitivity phenotype in human lymphocytes [115–118]. Furthermore, it was shown that it is also possible to use nucleoplasmic bridges (NPBs) to measure the radiation exposure dose [117,119,120]. The use of the lymphocyte CBMN assay for ionising radiation exposure biodosimetry, including triage biodosimetry, has now been validated by a large number of laboratories in interlaboratory comparison studies [121–123] and endorsed by the International Atomic Energy Agency and, furthermore, an ISO Standard on its application in the event of a radiation accident has been published [124,125]. MN studies with buccal cells were also frequently used to study the potential genotoxic and cytotoxic effect of electromagnetic radiation from mobile phones because of their proximity to the mobile phones when in use. The results of these investigations have been reviewed by Al-Serori et al. [126].

5.2. Chemical genotoxin exposure

It became evident early that the lymphocyte CBMN assay is sensitive *in vitro* to the genotoxic effects of a wide range of chemicals with different modes of actions, such as aneugens [127–129], radiomimetic agents [130], oxidants [131], methylating agents [132], DNA methylase inhibitors [133], nitrous oxide [134], heavy metals [135], advanced glycation end products [136], topoisomerase inhibitors [137]. Furthermore, numerous studies showed that *in vivo* exposure to genotoxicants caused MN formation *in vivo* and *ex vivo* in lymphocytes and *in vivo* in buccal cells [138–141]. The suitability of the lymphocyte CBMN assay to measure the DNA damaging effects of genotoxic chemicals has become widely recognised and led to the establishment of an OECD guideline on how to use the CBMN assay in peripheral blood lymphocytes and/or immortal lymphoblastoid cell lines for genotoxicity testing of chemicals [142]. It is important to note here that the lymphocyte CBMN assay and the buccal MN assay when used in cytome mode are in fact multi-endpoint assays that can also be used to measure other nuclear anomalies (such as NPBs and NBUDs) as well as apoptosis, necrosis and cytostatic effects [40,41,95,108,143]. Furthermore, molecular probes of the centromeres can also be used to distinguish between MN that contain chromosome fragments from MN that contain whole chromosomes [Fig. 3C] and, also, non-disjunction even in BN cells that do not contain MN [142–144].

In 2016 the HUMN project coordinated and published several review papers in a special issue on the use of the lymphocyte cytokinesis-block micronucleus (CBMN) assay to measure DNA damage induced *in vivo* in humans occupationally exposed to chemical genotoxins [145]. The papers reported progress and new research opportunities on a wide range of projects relating to this topic including, current knowledge of molecular mechanisms, systematic reviews and meta-analyses of epidemiological studies and a synthesis of the data from all the reviewed studies [146]. These studies either used the lymphocyte CBMN assay on its own or in combination with MN assays in other tissues and/or other DNA damage assays. A typical example is the HBM4EU study of occupational exposure to hexavalent chromium where MN in lymphocytes as well as reticulocytes and DNA strand breaks measured by comet assay were significantly increased in exposed subjects [147].

5.3. Genotoxic effects of malnutrition

Dawson and Bury were the first to show that folate and/or vitamin B12 deficiency causes the formation of Howell-Jolly bodies in red blood cells (RBCs) which were in fact MN originating from chromosome aberrations produced *in vivo* in erythroblasts in the bone-marrow of their patients [148]. It was later realised that the MN in erythroblasts are retained within RBCs after expulsion of the main nuclei, resulting in the formation RBCs containing MN in the peripheral blood [149,150]. Furthermore, it was shown that scoring MN in RBCs could be a useful biomarker of DNA damage in humans exposed to genotoxic agents or due to folate deficiency if they had their spleen removed [149,150]. A few years later it was shown that MN are also formed in lymphocytes of folate and/or B12 deficient humans [151–153]. The advantage of using the lymphocyte CBMN assay is that peripheral blood lymphocytes can be cultured for several days [14–21 days] which enables the study of the genotoxic effects of chronic micronutrient deficiency or excess under controlled conditions. For example, it was possible to study in detail the genotoxic effects of folate deficiency and riboflavin excess in cells which had genetic defects in the MTHFR gene relative to those that were normal and determine the interactive effects of the two micronutrients

with each other and the MTHFR genotype [154]. Details of the methodology of how to perform *in vitro* studies of the genomic effects of chronic micronutrient deficiency or excess using the CBMN assay were published by Bull et al. [155].

5.4. Automation

The acceptance of MN assays is assisted by the fact that MN are relatively easy to recognise and score in cells. However, two major challenges remain (i) the need to score 1000 or more cells for presence of MN depending on the required statistical power and (ii) the need to score MN exclusively in specific viable cells such as binucleated cells in the CBMN assay and differentiated mononuclear cells in the case of buccal cells. Furthermore, it is also desirable in the cytome mode of MN assays to also score other abnormal nuclear anomalies such NPBs and NBUDs and cells undergoing cell death such as necrosis and apoptosis in the case of the CBMN assay and cells with condensed chromatin, karyorrhectic cells, pyknotic cells, karyolytic cells in the case of buccal cells. The HUMN project conducted a workshop on MN assay automation which proposed a standardised system of validation and calibration to enable more reliable comparison of data across laboratories and across platforms and identified important limitations and steps that need to be taken into account to enable the successful universal implementation of automated micronucleus assays by image cytometry [156]. Automated scoring of MN in BN cells on glass slides has been achieved by a few companies using different image recognition algorithms [157–160]. More recently success in automation of MN assays using image flow cytometry has been reported using standard algorithms or AI assisted algorithms that can identify mono-, bi- or multinucleated cells with or without MN [161–163]. Analysis of MN in reticulocytes (i.e. immature erythrocytes), performed by flow cytometry, provides the simplest choice for an automated MN assay [164–166]. However up to now it has been performed only by a few laboratories and more research is required to validate this system with respect to its correlation with MN in buccal cells and lymphocytes and its association with disease risk both cross-sectionally and prospectively.

5.5. In vitro MN assays

Although the HUMN project is aimed at determining MN frequency in human populations and its health consequences it is also important to develop and validate *in vitro* and *ex vivo* MN assays that test the likely causes of MN induction *in vivo*. In this regard the HUMN project has been influential by standardising the *ex vivo* and *in vitro* lymphocyte CBMN assay systems protocols [41,44] which is critical because lymphocytes are unique in that they can be used not only to measure MN *in vivo* but also *ex vivo* and *in vitro*, Furthermore, the lymphocyte assay system is ideal because it can be used not only to study acute or chronic exposures to genotoxicants but it can also generate dose-response curves for biodosimetry, for example, in the case, of accidental exposure to ionising radiation [124,125]. In addition, assay systems with lymphocytes have also been developed to investigate the genotoxic effects of chronic exposure to micronutrient deficiency or excess [155] and also interactions between chemical genotoxin exposure and micronutrient deficiency [167,168]. The multi-parameter properties of the lymphocyte CBMN cytome assay make it ideal for *in vitro* genotoxicity testing [40,41] and it is for this reason that it has been adopted in the OECD test guideline #487 [142].

5.6. MN assays in other tissues

The HUMN project focused on the lymphocyte CBMN assay and the Buccal MN assay because at the time of its foundation these were the best validated methods that could be readily used to study MN frequency in human populations. However, as indicated in Fig. 1, MN assays in cells from other easily accessible tissues such as red blood cells, and epithelial tissues, such as nasal, cervical and urothelial cells have also been used successfully in studies of environmental carcinogenesis enabling comparisons of MN frequencies across multiple tissues. However, standardised protocols of MN assays in these tissues and their validation via inter-laboratory performance comparisons and association with occupational/environmental exposure to carcinogens and association with disease risk have not yet been adequately performed. The current "state of the art" of some of these alternative MN assays has been reported in some of the reviews contributed in HUMN project coordinated publications [169–172].

5.7. Mechanisms

An important aspect of the HUMN project was to synthesise current knowledge about the molecular mechanisms that lead to the formation of MN and other nuclear anomalies and their health consequences. These reviews were often published as part of special issues or books about MN in human cells. These reviews included mechanisms that lead to (i) MN formation following exposure to ionising radiation, chemical genotoxins, malnutrition, viral infection and (ii) the consequences including diseases caused by aneuploidy, diseases resulting from fragmentation of chromosomes trapped in MN leading to hypermutation of single chromosomes common in cancer and/or inflammation caused by leakage of DNA from MN into the cytoplasm via the cGAS-STING mechanism of the innate immune response [173–182]. An important aspect of this work is that a deeper understanding of the fate of MN in cells and that of cells that contain MN is necessary to fully appreciate the increasing relevance of MN as an indicator of cellular health [182,183].

5.8. Micronuclei and disease

The HUMN project produced a Special Issue (SI) on "Micronuclei and Disease" [184] to (i) Estimate level of evidence for the association of MN with likelihood of diseases in humans; (ii) Define mechanisms that may explain association of MN with each illness; and (iii) Identify knowledge gaps and research needed to translate use of MN assays into clinical practice. Majority of reviewed studies were case-control studies in which the ratio of mean MN frequency in disease cases relative to controls, i.e. the mean ratio (MR), was computed. The mean of these MR values, for lymphocyte MN and buccal cell MN in non-cancer diseases were 2.3 and 3.6 respectively, and for cancers they were 1.7 and 2.6 respectively. The highest MR values were observed in studies of cancer cases in which MN were measured in the same tissue as the tumour (MR = 4.9–10.8). These data, together with results from prospective cohort studies (see Section 3 last paragraph), are helping to identify illnesses, such as lung cancer, in which MN assays can be justifiably utilised to better identify high risk patients and to prioritise them for preventative therapy [185–187]. MN are amongst several biomarkers that can be used to predict disease risk.

5.9. Global impact leading to interactions with other relevant research networks

The activities of the HUMN project were of great interest to other networks utilising cytogenetic DNA damage biomarkers in their research such as the International Atomic Energy Agency (IAEA), European Study Group on Cytogenetic Biomarkers and Health (ESCH), Environmental Cancer Risk, Nutrition and Individual Susceptibility (ECNIS), the Realizing the European Network of Biological Dosimetry Project (RENEB), European network of research on nutrigenomics (NUGO), a European project investigating the role of prenatal and early-life exposure to genotoxic chemicals present in food and the environment in the development of childhood cancer (NewGeneris) and the Cytogenetic Biomarkers and Human Cancer Risk (Cancer Risk Biomarkers) research consortium.

5.10. Workshops/education

The HUMN project communicated its research plans and outcomes via workshops organised to coincide with conferences in the field of environmental mutagenesis such as: European Environmental Mutagenesis & Genomics Society (EEMGS), Environmental Mutagen Society of India (EMSI), International Conference of Environmental Mutagens (ICEM), International Conference of Environmental Mutagens in human populations (ICEMHP), United Kingdom Environmental Mutagenesis Society (UKEMS). In total 23 HUMN workshops were organised and conducted successfully in 15 different countries. For more details about the workshops please refer to Supplementary Table 2.

5.11. Special issues, book, publications and citations

It was recognised early that MN assays could be applied in diverse fields. Efforts were made to capture this emerging knowledge in special issues of relevant journals focused on specific topics relevant to the different fields of their application. A total of three special issues (SI) and one book, together containing 104 papers, were published as described in Table 1 below:

As indicated in Supplementary Table 1, at least 220 papers were published, in peer-reviewed journals, by HUMN project participants related to the objectives of the HUMN project. At least four of these papers [41,44,80,176] have been cited more than 1000 times according to Google Scholar.

Table 1
Special Issues and book published by HUMN project participants.

Title of SI or Book	Journal, Publishers	Date of publication, Volume, pages,	Editor/s	No. of papers *
SI: Micronuclei – Recent advances in their measurement, in understanding molecular mechanisms, and their association, with environment, genetics and disease	Mutagenesis, Oxford University Special 25th Anniversary Issue of Mutagenesis. Dedicated to James M Parry	January 2011, Vol 26 (1) Pages 1–247	M. Fenech	35
SI: In vivo chemical genotoxin exposure and DNA damage in humans measured using the lymphocyte cytokinesis-block micronucleus assay	Mutation Research (Reviews), Elsevier	Oct/Dec 2016, Vol 770 (Part A), Pages 1–216,	S. Knasmueller, A. Nersesyan, M. Fenech	16
SI: Micronuclei and Disease	Mutation Research (Reviews in Mutation Research), Elsevier	2022 Vol 789F1	S. Bonassi, K. H. Wagner, M. Fenech	15
Book: The Micronucleus Assay in Toxicology	Issues in Toxicology, The Royal Society of Chemistry	2019, Issues in Toxicology No.39 Pages 1–648	Siegfried Knasmueller and Michael Fenech	38

* References to papers in these special issues and book are in Supplementary Table 1.

6. Lessons learnt and knowledge gaps that still need to be addressed

The success of the HUMN project was driven by the need for a relatively simple and robust cytogenetic method to measure DNA damage in humans that was practical and not too expensive to implement. The HUMN project facilitated this by developing practical protocols to measure MN in lymphocytes and buccal cells and then communicating these via the HUMN workshops. This enabled harmonisation of the application of these methods internationally. Furthermore, the contribution of numerous laboratories of MN data from individuals unexposed or exposed to environmental mutagens or afflicted with different diseases enabled epidemiological studies that provided important insights on the cross-sectional and prospective association of MN with environmental genotoxins exposure and disease risk. Furthermore, a large data base of "normal" base-line values has enabled the establishment of normal reference values of MN frequency observed in healthy people indicating an achievable lower level of DNA damage that may be required to minimise disease risk in human populations.

To maintain this momentum and improve the applicability of MN assays to human health promotion it is necessary to continue research enabling a better understanding of the molecular mechanisms underlying the biology and pathology of MN and other associated nuclear anomalies such as nucleoplasmic bridges and nuclear buds. In this regard, it is desirable that these additional biomarkers that are available when using the MN assays in cytome mode are also scored. To enable this, advanced automated scoring system using artificial intelligence will need to be developed. Recent reports indicate that this approach is likely to be feasible (see Section 5.4).

The initiatives of the HUMN project have also led to the much greater appreciation of the interconnectedness of the various cytological nuclear anomalies (e,g, MN, NPB, NBUD), the strong correlations with each other under different genotoxic stresses and the mechanisms that explain their common origin from induced DNA lesions, DNA mis-repair and chromosome aberrations. This emphasises the importance of carefully studying the impact of genotoxic stressors, including malnutrition, not only at the molecular level but also at the cellular/nuclear level because ultimately the health of tissues and organs and the whole organism depends on cellular genome health. It is also for this reason that one of the outcomes of the HUMN project has been the Genome Health Clinic concept based on diagnosis and prevention of DNA damage and the concept that dietary recommendations for human health should also be based on DNA damage prevention [188,189].

The HUMN activities of standardising and validating lymphocyte MN methods resulted in their adoption world-wide and, importantly, also led to international regulations and guidelines for *in vitro* MN genotoxicity testing of chemicals and for *in vivo* ionising radiation exposure biodosimetry. Further efforts are now required to establish regulatory guidelines on the use of erythrocyte, lymphocyte and buccal MN assays for measuring *in vivo* DNA damage caused by occupational, nutritional, lifestyle or environmental exposure to chemical genotoxins, both individually and as complex mixtures.

Our experience in developing and sustaining the HUMN project over more than 25 years has reflected and verified important aspects of success including (i) The power of an idea whose time has come. (ii) The power of international collaboration. (iii) The Importance of understanding the biology of MN and other nuclear aberrations across different tissues. (iv) The importance of discovering and understanding the variables affecting MN frequency and (v) Commitment to achievable goals in the short and in the longer term. Figs. 5 and 6 illustrate the timeline of HUMN project achievements with the lymphocyte CBMN assay and the buccal MN technique.

Despite these efforts several knowledge gaps still need to be

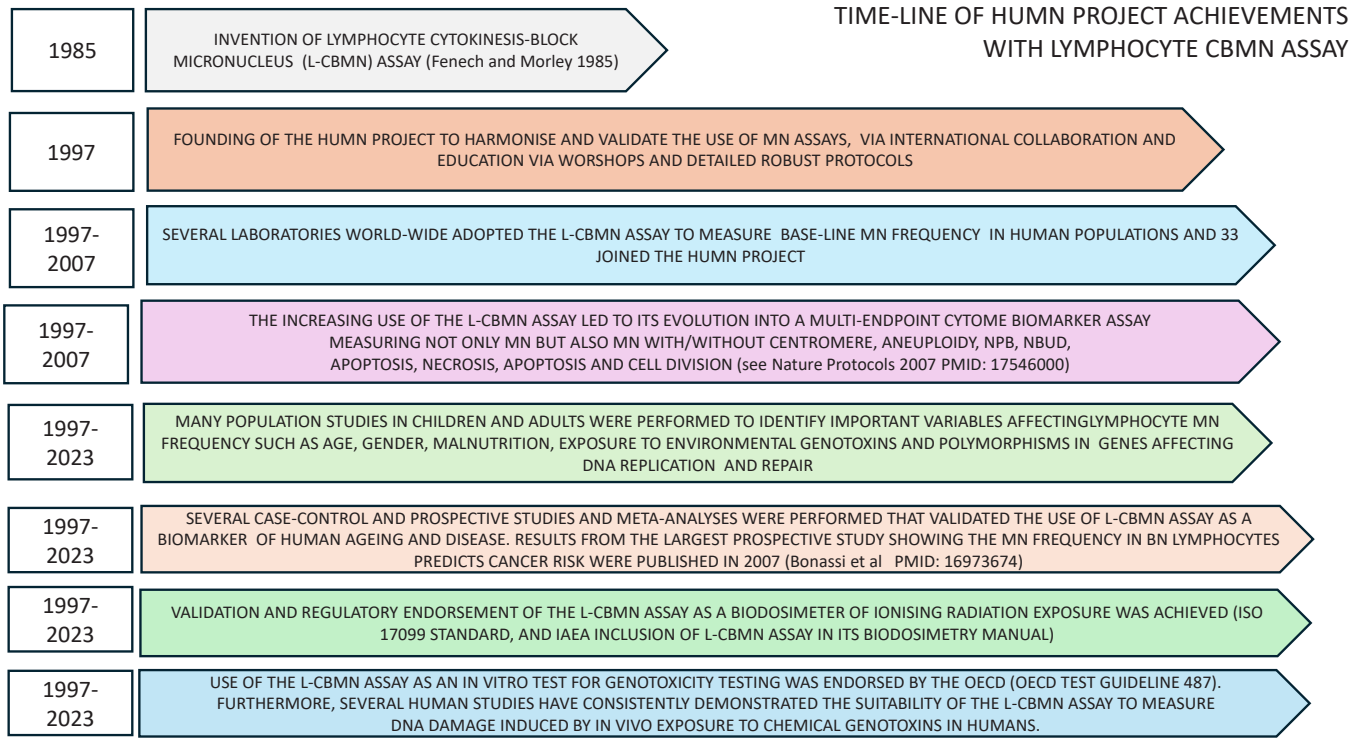

Fig. 5. Timeline of HUMN project achievements with lymphocyte CBMN assay.

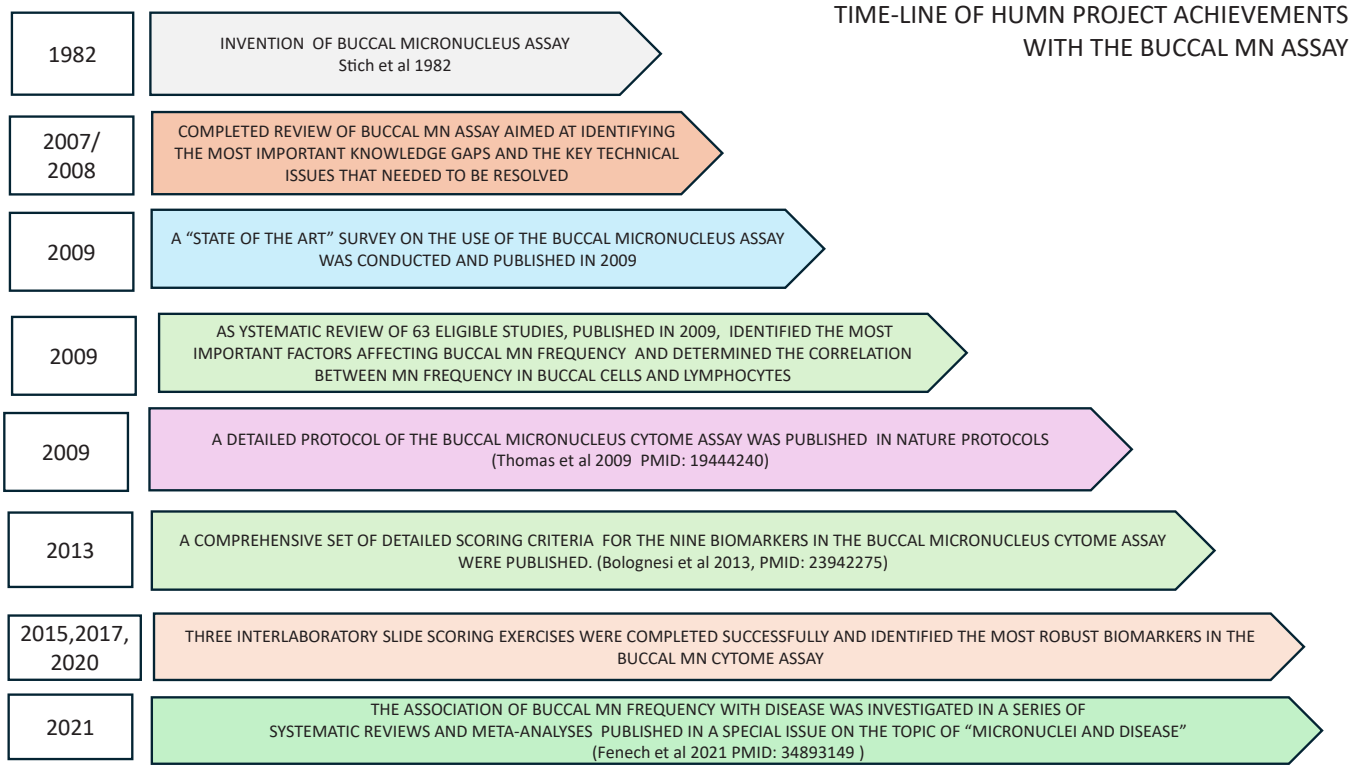

Fig. 6. Timeline of HUMN project achievements with buccal MN assay.

addressed such as (i) Are buccal MN predictive of disease risk? (ii) How can we translate the use of lymphocyte and buccal MN assays and the data they generate in the clinical setting and public health policy? (iv) Should MN assays be done not only in humans but also in sentinel species to enable a more biodiverse ecosystem approach for DNA damage biomonitoring? and (v) Is automated scoring of MN and other nuclear anomalies based on AI essential to facilitate MN data collection?

Declaration of Competing Interest

None.

Data Availability

The authors do not have permission to share data.

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The authors consisted of the founding members of the HUMN project and other members who joined the HUMN project over the 26-year period via their roles as chief investigators of projects done in collaboration with the HUMN project.

The list of references includes mainly papers co-authored by members of the HUMN project who collaborated together to meet the project objectives.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mrrev.2024.108511.

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