Supplementary Materials for

Lack of transgenerational effects of ionizing radiation exposure from the Chernobyl accident

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Published 22 April 2021 on *Science* First Release
DOI: 10.1126/science.abg2365

This PDF file includes:

Other Supplementary Materials for this manuscript includes the following:
(available at science.sciencemag.org/cgi/content/full/science.abg2365/DC1)

MDAR Reproducibility Checklist (.pdf)
Table S1 (.xlsx)

Materials and Methods

Chernobyl accident study population

Trio samples for this investigation come from the NCI-RCRM Trio Study (*27*). This joint study of the Division of Cancer Epidemiology and Genetics of the US National Cancer Institute (NCI) and the National Research Center for Radiation Medicine (NRCRM) in Kiev (Kyiv in Ukrainian) was designed to investigate potential genomic changes associated with ionizing radiation exposure resulting from the Chernobyl accident. Trio recruitment was conducted by NRCRM to identify trios in which parents were externally exposed to varying levels of ionizing radiation either as radiation cleanup workers or evacuees from areas contaminated by the Chernobyl disaster. Included trios were selected from a representative Chernobyl population of exposed individuals that are part of NRCRM's Clinico-Epidemiologic Registry. To participate, trios were required to have offspring that were at least 18 years of age at study recruitment and born 46 or more weeks after the last substantial parental exposure to Chernobyl-related ionizing radiation. Among these 105 trios there were 5 cancer cases (4 fathers and 1 mother). In an effort to enhance the spectrum of parental exposures recruited for study, five exposure categories were targeted for participation: (1) exposed father only, (2) exposed mother only, (3) both parents exposed, (4) high dose emergency workers, some of which experienced acute radiation syndrome and (5) neither parent exposed. The 105 trios evaluated in this study were selected from 152 reported trios (*26*); after the exclusion of two children, one as a QC failure and one was determined as non-paternity, the final data set included 130 children. Trio parents were interviewed to complete a general questionnaire to collect data on demographics, non-radiation risk factors, cancer diagnoses, smoking history, alcohol consumption, hazardous exposures and work history and were asked to provide blood and buccal samples. The study was reviewed and approved by the NRCRM IRB in Ukraine and all trio study participants provided informed consent.

Dosimetry estimation

Parents were interviewed by trained interviewers and were asked to provide detailed information on work history and activities in the 70-kilometer zone surrounding the Chernobyl Nuclear Power Plant. Interview data were reviewed and interpreted by a dosimetrist who incorporated knowledge from databases of radiation fields in the environment and his own experience as a Chernobyl cleanup worker. Cumulative doses to the parental gonads were reconstructed from the time of the April 26, 1986 accident up until 38 and 51 weeks before the offspring's date of birth. Resulting doses were estimated for three components of ionizing radiation exposure: (1) external irradiation during cleanup work, (2) external irradiation from residing in Pripyat, and (3) external irradiation and ingestion of cesium isotopes (^{134}Cs and ^{137}Cs) during residence in the settlements other than Pripyat. Rockville computer code, a further development of Realistic Analytical Dose Reconstruction with Uncertainty Estimation (RADRUE) (*40*) was used for cumulative dose reconstruction of doses due to external irradiation during cleanup work and residence in Pripyat. A special computer code was designed to calculate doses and associated uncertainties for residence in the settlements other than Pripyat with dose to the gonads estimated from both external and internal exposure. Full details of the dosimetry methods and dose uncertainty are available in Chumak et al. (*26*).

Variant calling pipeline

Aligned whole genome sequencing BAM files were received in four sets from the Broad Institute. The first three sets (n=214 subjects; referred to below as "Batch 1") were received aligned to hg19, while the fourth set (n=126 subjects; referred to below as "Batch 2") was aligned to hg38. Genome Analysis Toolkit (GATK) HaplotypeCaller module was run on each trio to call germline variants. Resultant trio VCF files were processed using GATK PhaseByTransmission module and Mendelian inconsistency errors (MIEs) were identified for each mother/father/child trio.

de novo mutation (DNM) filtering strategy

Because the input to most de novo mutation (DNM) filtering pipelines is variants that manifest as Mendelian inconsistency errors (MIE calls, see **Figure S6**), the vast majority of them represent QC issues and determining true DNMs from noise is challenging. We evaluated 17 tools developed for detecting DNMs and/or manuscripts describing their detection, then tuned our MIE filtering strategy using two approaches: Wong et al. 2016 (*8*) and Epi 4K Consortium et al. 2013 (*28*). Through iterative benchmarking experiments on six mother/father/child trios, the Wong et al. (*8*) method resulted in an excess of false negatives and the Epi et al. 2013 (*28*) method produced an excess of false positives based on IGV (*41*,*42*) review of the results. Therefore, we employed a modified version of the Wong et al. (*8*) method for main analyses. MIEs were filtered using the following criteria modified from Wong et al. (*8*): Phred-scaled genotype likelihoods (PL) for AA genotype is 0 for both parents; PL for AB is 0 for child; read depths for each individual in the trio must be ≥ 10; transmission probability > 20, reads for ALT and REF in child ≥ 5; and >30% of reads support ALT in child. All variants passing these filters were manually inspected in IGV (*41, 42*) and assigned a disposition (for example, real or noise). Parent-of-origin was assigned, when possible, with GATK ReadBackedPhasing module using the trio BAM files and the output from PhaseByTransmission and/or manually. A modified version of Maruvka et al. (2017) (*43*) was leveraged in the identification of a subset of indels. For male chromosome X DNMs, homozygous alternative allele MIEs were triaged and inspected for validity.

Figure S7 shows the performance of each pipeline compared to the number of DNMs reported in the manuscript ("Batch#-DNM-N," pinkish-purple line). Note that the numbers are normalized to those generated using the parameters from the Wong et al. (*8*) ("MDNMv1") original pipeline. The unmodified MDNMv1 pipeline produced high levels of false negatives, while both modified versions (MDNMv2, MDNMv3), and Epi 4K Consortium et al. (*28*) (Epi) methods resulted in an excess of false positives (**Figure S7**). False negative variants from MDNMv1 were primarily due to a filter limiting the upper limit on depth (≤100 reads), which is appropriate for 30x coverage but too restrictive at ~80x

coverage, as well as a restrictive rule that the alternative allele count is zero in the child, which also is too strict for 80x coverage, as sometimes one or two reads may randomly contain an alternate base. Manual review in IGV (*41*,*42*) was critical in reporting accurate numbers in all cases, but particularly since Batch 2 resulted in much noisier results **Figure S7**.

Assessment of sequencing batches

Whole-genome sequencing (WGS) was performed at Broad Institute and received in two forms: Batch 1, Illumina X10 sequencing, alignment to GRCh37/hg19 - 214 subjects; and Batch 2, Illumina NovaSeq sequencing, alignment to GRCh38 - 126 subjects. Ten individuals from three families (two trios and one quad) that were sequenced in Batch 1 were submitted to Broad for WGS and alignment under the same conditions as Batch 2. All subsequent processing steps were completed identically through our filtering pipelines (see above) for both batches.

Overall, agreement between the two batches was very high. **Table S10** shows the total number of variants reported for each of the four children in the set by variant type and includes numbers of false positives and negatives relative to Set 1. For example, for Subject 1 (GDC ID= UTRI_SUBJECT_001_000054), as reported in the manuscript, this individual had a total of 104 DNMs: 75 SNVs, 26 indels, 2 clusters, and 1 complex variant. Because the two clusters and one complex variant consisted of eight separate variants, this individual has a total of 109 called variants (see **Table S1**). In the Batch 1 vs Batch 2 comparison, most of the DNMs were identified in both batches but a few set differences were noted: one SNV and three indels from the original V1 set were determined to be false positives. 12 variants were newly identified in Batch 2 and were therefore false negatives with respect to Batch 1, including four SNVs, six indels, one cluster, and one complex variant (**Table S10**). Similar patterns were observed for the other three individuals (**Table S10**), with fewer false positives in Batch 2 and small numbers of new variants detected (false negatives from Batch 1).

The dearth of false positives in the Batch 1 data set is most likely due to two main factors: 1) an average of 80x sequencing depth at all sites and 2) the manual review of each variant in IGV (*41,42*). False negatives in Batch 1 that were detected in Batch 2 may be due to improved sequencing chemistry (HiSeq vs. NovaSeq) and/or an improvement in the reference assembly (hg19 vs. b38). Additionally, the overall high concordance for more than 350 DNMs across four individuals between WGS runs is reassuring. Although not strictly orthogonal validation, such high agreement suggests robust, reproducible results in our study.

Telomere length assay

Quantitative polymerase chain reactions (qPCR) were used to measure relative telomere length by measuring the ratio of telomere TTAGGG repeat sequence signal (T) to single copy gene (36B4) signal (S) to yield relative standardized T/S ratios of telomere length. Primers for the telomeric assay were TeloFP [5'-CGGTTT(GTTTGG)5GTT-3'] and TeloRP [5'-GGCTTG(CCTTAC)5CCT-3'] and for the single-copy gene assay were 36B4_FP [5'-CAGCAAGTGGGAAGGTGTAATCC-3'] and 36B4_RP [5'-CCCATTCTATCATCAACGGGTACAA-3'] (*33, 44*). Primers were normalized to 100 µM in IDTE, pH 8.0 and purified by HPLC (Integrated DNA Technologies). 1 µM assay mixes were generated by combining 990 µL of 1X Tris-EDTA Buffer with 5 µL of forward oligo and 5 µL of reverse oligo. PCR was performed using a 5 µL reaction volume as follows: 2.5 µL of 2X Rotor-Gene SYBR Green PCR Master Mix (QIAGEN), 2.0 µL of MBG Water, and 0.5 µL of 1 µM assay-specific mix. For each reaction, 4 ng of sample DNA was used. Thermal cycling was performed on a LightCycler 480 (Roche) where PCR conditions were (i) T (telomeric) PCR: 95˚C hold for 5 min, denature at 98˚C for 15 s, anneal at 54˚C for 2 min, with fluorescence data collection, 35 cycles and (ii) S (single-copy gene, 36B4) PCR: 98˚C hold for 5 min, denature at 98˚C for 15 s, anneal at 58˚C for 1 min, with fluorescence data collection, 43 cycles. A standard curve from 6 concentrations of pooled reference DNA samples prepared by serial dilution (4 to 0.04096 ng/uL) and randomly located internal QC sample replicates (n=5) were utilized as calibrator samples to guide

analysis and indicate overall assay performance. Additionally, no template controls were added to random well locations to provide a fingerprint for each plate. All samples were assayed in triplicate for both assays. We used the LightCycler software (Release 1.5.0) to generate Ct values utilizing the absolute quantification analysis with the second derivative maximum method and high sensitivity detection algorithm. If meeting a CV threshold of less than 2%, Ct values of replicates were averaged and the concentration (ng/µL) was interpolated from the plate-specific standard curve's exponential regression [Average Ct and log2(Concentration)]. Any sample with 36B4 concentrations falling outside the range of the standard curve was dropped from further analysis. The raw T/S ratio was divided by the average raw T/S ratio of the internal QC calibrator samples, within the same plate set, to yield a standardized T/S ratio to normalize results in reference to the same individual. Z-scores were calculated to adjust RTL to account for batch differences.

Statistical Analysis

Average DNMs per genome was calculated by summing all mutations in an analytic group of interest and dividing by the total number of children in the analytic group. Analyses of cumulative maternal and paternal ionizing radiation dose utilized continuous estimated dose values. All models used in the analysis of DNMs were multivariable adjusted linear regression models with adjustments for sequencing batch, paternal and maternal age, and paternal and maternal smoking status. A series of sensitivity analyses were conducted to evaluate doses truncated at 1Gy as well as using log transformed dose values by adding 1 mGy to the dose and taking the natural logarithm (**Table 3**). In addition, multivariable linear regression models with robust standard errors (sandwich estimator) and Poisson regression (quasi-likelihood with an estimated scale term to account for overdispersion) were used to avoid the assumption of normally distributed error terms with constant residual variances. All of these analyses resulted in similar results (**Table S8** and **Table S9**).

Principal components analysis to determine population structure (**Figure S1**) was run using smartpca (from EIGENSOFT v6.1.4, (*45*)) with outliers flagged at >6 sd.

All statistical analyses were performed in the R statistical software. The correlation plots of related covariates were generated using the corrplot package. DNM and telomere length analyses were performed using R version 3.6.1 (2019-07-05; "Action of the Toes") on macOS Mojave version 10.14.6.

Supplementary Tables and Figures

Table S1. Individual level data for detected DNMs and analytic variables.

Data available in separate downloadable .xlsx file.

Table S2. Descriptive characteristics of Chernobyl trios.

	Mean	Median	Range	Standard Deviation
Age at Conception				
Maternal	26.76	26	18-39	5.20
Paternal	29.22	28	18-52	5.71
Ionizing Radiation Exposure (mGy)				
Maternal	19.29	2.10	0.13-550	71.63
Paternal	365.41	29.26	0-4,080	684.55

	Count	Percentage
Child's Birth Year		
1987-1989	45	34.6%
1990-1994	56	43.1%
1995-2002	29	22.3%
Child's Sex		
Female	58	44.6%
Male	72	55.4%
Smoking History at Conception		
Maternal Never Smoker	106	81.5%
Maternal Former Smoker	10	7.7%
Maternal Current Smoker	14	10.8%
Paternal Never Smoker	44	33.8%
Paternal Former Smoker	13	10.0%

Paternal Current Smoker	65	50.0%
Paternal Unknown	8	6.2%

Table S3. Distribution of paternal and maternal ionizing radiation doses.

	0-<25mGy		25-<100mGy		100-<500mGy		500-<1000mGy		1000+mGy		Total	
	N	%	N	%	N	%	N	%	N	%	N	%
Paternal dose	63	*48%*	13	*10%*	24	*18%*	13	*10%*	17	*13%*	130	*100%*
Child's year of birth												
1987	7	*54%*	1	*8%*	2	*15%*	2	*15%*	1	*8%*	13	*100%*
1988-89	13	*41%*	2	*6%*	9	*28%*	4	*13%*	4	*13%*	32	*100%*
1990-94	22	*39%*	7	*13%*	10	*18%*	7	*13%*	10	*18%*	56	*100%*
1995-2002	21	*72%*	3	*10%*	3	*10%*	0	*0%*	2	*7%*	29	*100%*
Paternal age at exposure												
12-19y	18	*69%*	2	*8%*	3	*12%*	0	*0%*	3	*12%*	26	*100%*
20-24y	31	*58%*	6	*11%*	7	*13%*	5	*9%*	4	*8%*	53	*100%*
25-29y	9	*27%*	1	*3%*	11	*33%*	4	*12%*	8	*24%*	33	*100%*
30-34y	4	*29%*	4	*29%*	2	*14%*	2	*14%*	2	*14%*	14	*100%*
35-41y	1	*25%*	0	*0%*	1	*25%*	2	*50%*	0	*0%*	4	*100%*
Paternal age at conception												
18-24y	19	*66%*	2	*7%*	5	*17%*	1	*3%*	2	*7%*	29	*100%*
25-29y	22	*43%*	5	*10%*	10	*20%*	6	*12%*	8	*16%*	51	*100%*
30-34y	13	*42%*	4	*13%*	5	*16%*	3	*10%*	6	*19%*	31	*100%*
35-39y	7	*58%*	1	*8%*	1	*8%*	2	*17%*	1	*8%*	12	*100%*
40-51y	2	*29%*	1	*14%*	3	*43%*	1	*14%*	0	*0%*	7	*100%*

Table S3, cont.

	0-<25mGy		25-<49mGy		50-99mGy		100-<500mGy		500+mGy		Total	
	N	***%***	**N**	***%***	**N**	***%***	**N**	***%***	**N**	***%***	**N**	***%***
Maternal dose	116	*89%*	5	*4%*	6	*5%*	1	*1%*	2	*2%*	130	*100%*
Child's year of birth												
1987	12	*92%*	0	*0%*	1	*8%*	0	*0%*	0	*0%*	13	*100%*
1988-89	30	*94%*	1	*3%*	1	*3%*	0	*0%*	0	*0%*	32	*100%*
1990-94	49	*88%*	2	*4%*	2	*4%*	1	*2%*	2	*4%*	56	*100%*
1995-2002	25	*86%*	2	*7%*	2	*7%*	0	*0%*	0	*0%*	29	*100%*
Maternal age at exposure												
10-19y	43	*88%*	3	*6%*	3	*6%*	0	*0%*	0	*0%*	49	*100%*
20-24y	41	*95%*	0	*0%*	1	*2%*	1	*2%*	0	*0%*	43	*100%*
25-29y	28	*93%*	2	*7%*	0	*0%*	0	*0%*	0	*0%*	30	*100%*
30-33y	4	*50%*	0	*0%*	2	*25%*	0	*0%*	2	*25%*	8	*100%*
Maternal age at conception												
18-24y	49	*88%*	3	*5%*	4	*7%*	0	*0%*	0	*0%*	56	*100%*
25-29y	33	*97%*	0	*0%*	0	*0%*	1	*3%*	0	*0%*	34	*100%*
30-34y	25	*89%*	1	*4%*	2	*7%*	0	*0%*	0	*0%*	28	*100%*
35-39y	9	*75%*	1	*8%*	0	*0%*	0	*0%*	2	*17%*	12	*100%*

Table S4. Parent-of-origin estimates for age at conception and cumulative radiation dose. Estimates are for the 42% of DNMs where phase could be determined based on an informative nearby germline variant(s) on a parental haplotype. Separate models were fit to estimate paternal and maternal effects. Dose estimates are for continuous dose measured in mGy. All models were additionally adjusted for sequencing batch and parental smoking status at conception.

	Estimate	95% Confidence Interval	P-value
Paternal Origin DNMs			
Paternal Age	0.71	0.54, 0.88	3.67E-13
Paternal Dose (mGy)	-0.001	-0.002, 0.0005	0.20
Maternal Origin DNMs			
Maternal Age	0.28	0.15, 0.40	3.24E-05
Maternal Dose (mGy)	0.001	-0.008, 0.01	0.77

Table S5. Effect estimates of cumulative radiation dose on subgroups of DNMs. Total DNMs merge all the DNM subgroups together for a combined analysis and Microsatellites are a further subgrouping of Indels. Separate models are run for each subgroup. Dose estimates are for continuous dose measured in mGy. All models additionally adjust for sequencing batch, parental age, and parental smoking status.

	Estimate	95% Confidence Interval	P-value
Clusters (n = 181)			
Paternal Dose (mGy)	-0.0002	-0.0005, 0.0002	0.33
Maternal Dose (mGy)	0.003	-0.0008, 0.006	0.13
Complex (n = 50)			
Paternal Dose (mGy)	0.00001	-0.0002, 0.0002	0.91
Maternal Dose (mGy)	-0.0003	-0.002, 0.002	0.73
Indels (n = 2,103)			
Paternal Dose (mGy)	0.0002	-0.001, 0.001	0.78
Maternal Dose (mGy)	-0.01	-0.02, 0.002	0.12
Microsatellites (n = 730)			
Paternal Dose (mGy)	0.0003	-0.0004, 0.001	0.41
Maternal Dose (mGy)	-0.002	-0.008, 0.004	0.51
SNVs (n = 9,388)			
Paternal Dose (mGy)	-0.0008	-0.003, 0.002	0.51
Maternal Dose (mGy)	-0.01	-0.03, 0.01	0.39
Total DNMs (n = 11,722)			
Paternal Dose (mGy)	-0.0007	-0.003, 0.002	0.56
Maternal Dose (mGy)	-0.02	-0.04, 0.007	0.17

Table S6. Examination of impact of parental radiation dose categories on DNMs. Linear regression models are used with dose categories as detailed in **Table S3**. The lowest dose group was used as the reference. The model was additionally adjusted for sequencing batch, maternal and paternal age, and maternal and paternal smoking status.

	Effect	**95% CI**	**P-value**
Paternal Dose			
0-<25mGy	(reference)		
25-<100mGy	2.75	-3.37, 8.88	0.37
100-<500 mGy	-1.2	-6.29, 3.90	0.64
500-<1000 mGy	-5.03	-11.35, 1.30	0.12
1000+ mGY	-0.99	-6.48, 4.51	0.72
Maternal Dose			
0-<25mGy	(reference)		
25-<50mGy	-2.56	-11.93, 6.82	0.59
50-<100mGy	-2.58	-10.63, 5.46	0.53
100-<500mGy	-5.11	-25.79, 15.56	0.63
500+ mGY	-6.98	-21.59, 7.62	0.35

Table S7. Multivariate associations for qPCR measured standardized relative telomere length in leukocytes of trio children.

	Estimate	Std. Error	p-value
Child characteristics			
Age at blood draw	1.89E-03	2.95E-03	0.52
Sex (female=0, male=1)	-1.70E-02	1.80E-02	0.35
Former smoker	2.40E-02	2.96E-02	0.42
Current smoker	1.24E-02	2.32E-02	0.60
Age at conception			
Paternal Age	1.32E-04	2.21E-03	0.95
Maternal Age	4.62E-03	2.41E-03	0.06
Cumulative log radiation dose			
Paternal Dose	2.03E-06	1.32E-05	0.88
Maternal Dose	-2.75E-04	1.24E-04	0.03
Smoking history at conception			
Paternal former smoker	2.02E-02	3.15E-02	0.52
Paternal current smoker	2.26-03	1.97E-02	0.91
Maternal former smoker	5.27E-02	3.61E-02	0.15
Maternal current smoker	-3.52E-02	2.86E-02	0.22

Table S8. Assessment of modeling approaches on the association between dose and DNMs. All models adjust for sequencing batch, paternal and maternal age, and paternal and maternal smoking status. Dose is modeled in the continuous mGy scale, except where noted. The linear model with robust variance uses a sandwich estimator that results in valid statistical inference under departures from normal error and constant variance (relative to mean). The Poisson regression model uses an estimated scale parameter (quasi-likelihood). All estimates from Poisson models are interpreted as the log proportional change in mutation count per unit change in dose.

	Estimate	Standard Error	95% Confidence Interval	P-value
Linear Model				
Paternal Dose (mGy)	-0.0007	0.0013	-0.0033, 0.0018	0.56
Maternal Dose (mGy)	-0.0170	0.0123	-0.0412, 0.0071	0.17
Linear Model (robust variance)				
Paternal Dose (mGy)	-0.0007	0.0018	-0.0043, 0.0028	0.68
Maternal Dose (mGy)	-0.0170	0.0134	-0.0433, 0.0092	0.20
Poisson Model (with overdispersion)				
Paternal Dose (mGy)	-5.94E-06	1.43E-05	-3.40E-05, 2.21E-05	0.68
Maternal Dose (mGy)	-1.76E-04	1.36E-04	-4.43E-04, 9.10E-05	0.20

Table S9. Assessment of modeling approaches on the association between age and DNMs. All models adjust for sequencing batch, paternal and maternal dose, and paternal and maternal smoking status. Dose is modeled in the continuous mGy scale, except where noted. The linear model with robust variance uses a sandwich estimator that results in valid statistical inference under departures from normal error and constant variance (relative to mean). The Poisson regression model uses an estimated scale parameter (quasi-likelihood). All estimates from Poisson models are interpreted as the log proportional change in mutation count per one-year increase in age.

	Estimate	Standard Error	95% Confidence Interval	P-value
Linear Model				
Paternal Age	1.9360	0.2143	1.5159, 2.3561	3.65E-15
Maternal Age	0.4569	0.2390	-0.0116, 0.9254	0.06
Linear Model (Robust Variance)				
Paternal Age	1.9360	0.1956	1.5527, 2.3193	4.21E-23
Maternal Age	0.4569	0.2508	-0.0346, 0.9484	0.07
Poisson Regression (with overdispersion)				
Paternal Age	0.0195	0.0022	0.0151, 0.0239	2.35E-14
Maternal Age	0.0053	0.0026	0.0003, 0.0104	0.04

Table S10. A comparison of results from four children from three families sequenced, along with their parents, under conditions for both Batches 1 and 2.

	Subject 1 n = 104 (109)‡			**Subject 2 n = 98 (100)‡**			**Subject 3 n = 84 (90)‡**			**Subject 4 n = 70 (72)‡**		
DNM type	# reported‡	false +	false -	# reported‡	false +	false -	# reported‡	false +	false -	# reported‡	false +	false -
SNV	75	1	4	84	0	0	68	2	4	56	0	2
indel	26	3	6	13	0	6	11	1	8	12	0	5
cluster	2 (6)‡	0	1 (2)‡	1 (2)‡	0	0	4(8)‡	0	0	2(4)‡	0	0
complex	1 (2)‡	0	1 (2)‡	0	0	0	1 (3)‡	0	0	0	0	0

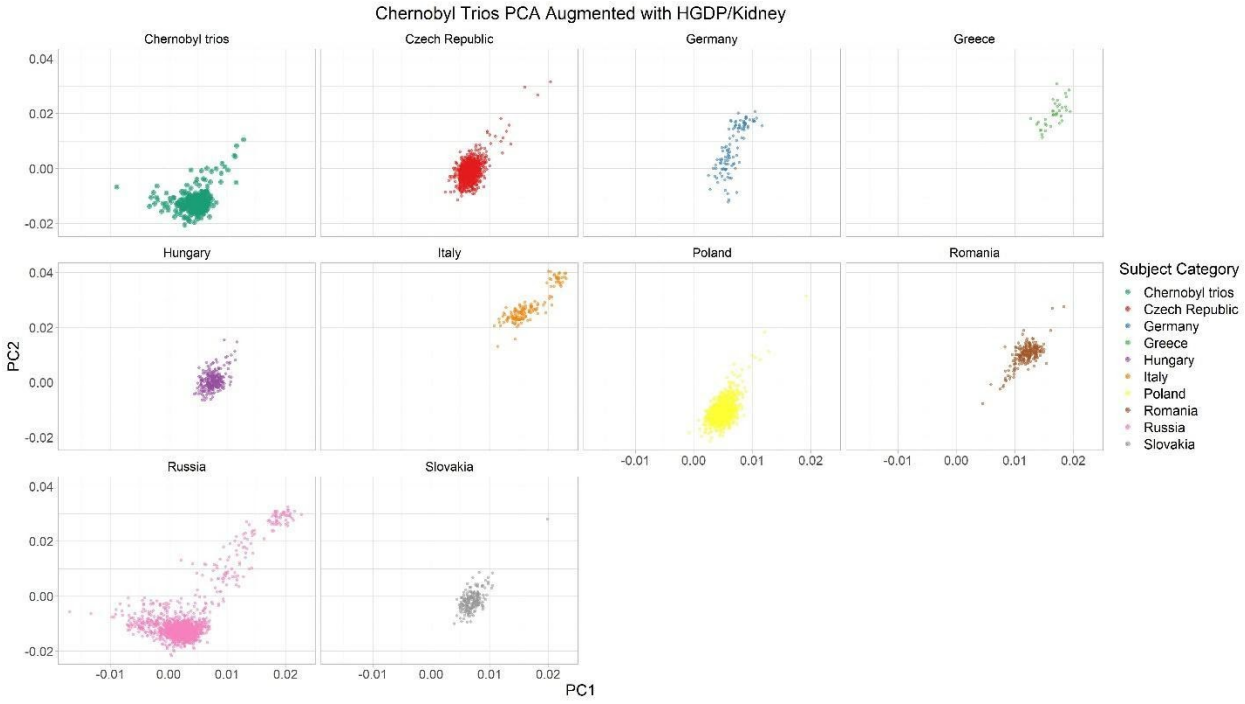
- #(#) corresponds to number of DNMs counted for analyses (# of total variants represented)

From Table S2:

Subject 1 = GDC_ID UTRI_SUBJECT_001_000054; Subject 2 = GDC_ID UTRI_SUBJECT_001_000118

Subject 3 = GDC_ID UTRI_SUBJECT_001_000483; Subject 4 = GDC_ID UTRI_SUBJECT_001_000484

Figure S1. Principal Components Analysis (PCA) showing the relationships among the Chernobyl trio subjects versus others from Eastern European countries. Subjects were drawn from a prior publication(*46*) that included Czech Republic, n = 902; Germany, n = 108; Greece, n = 36; Hungary, n = 259; Italy*, n = 139; Poland, n = 1075; Romania, n = 228; Russia*, n = 1593; and Slovakia, n = 209.



*For Italy and Russia, 48 and 42 subjects, respectively, from the Human Genome Diversity Panel(*47*) were also included in the totals.

Figure S2. Correlation of paternal and maternal dose with DNMs. Measures of DNMs include overall DNMs, DNMs corrected for paternal age, DNMs corrected for maternal age, DNMs corrected for both paternal and maternal age (parental age) and the full model adjusting for sequencing batch, parental age and parental smoking status.

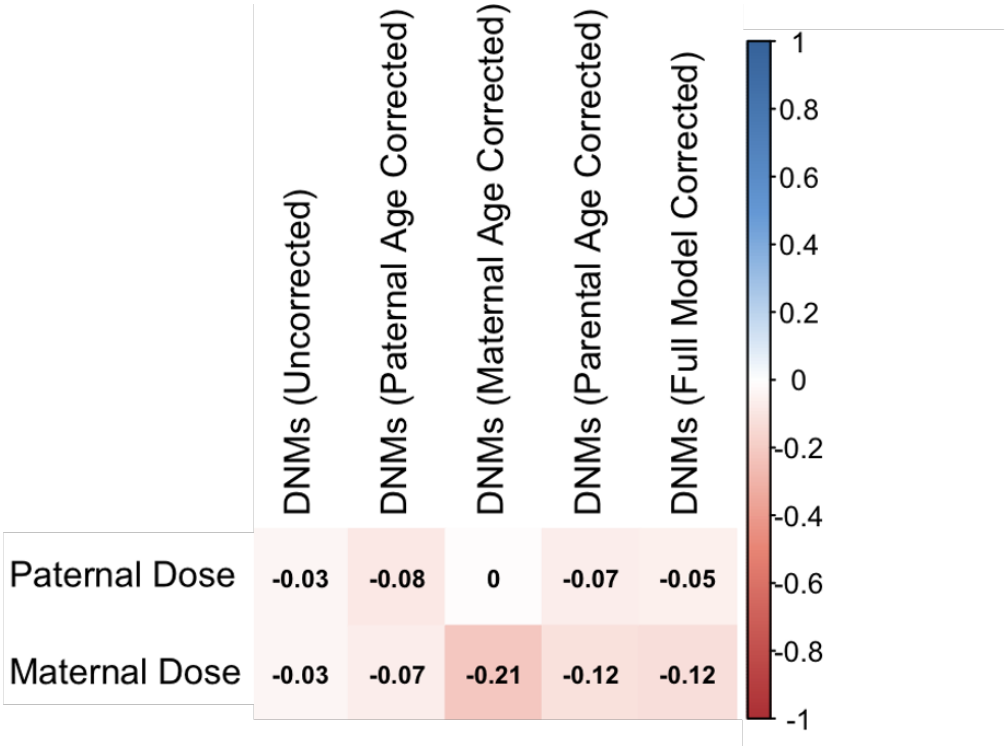
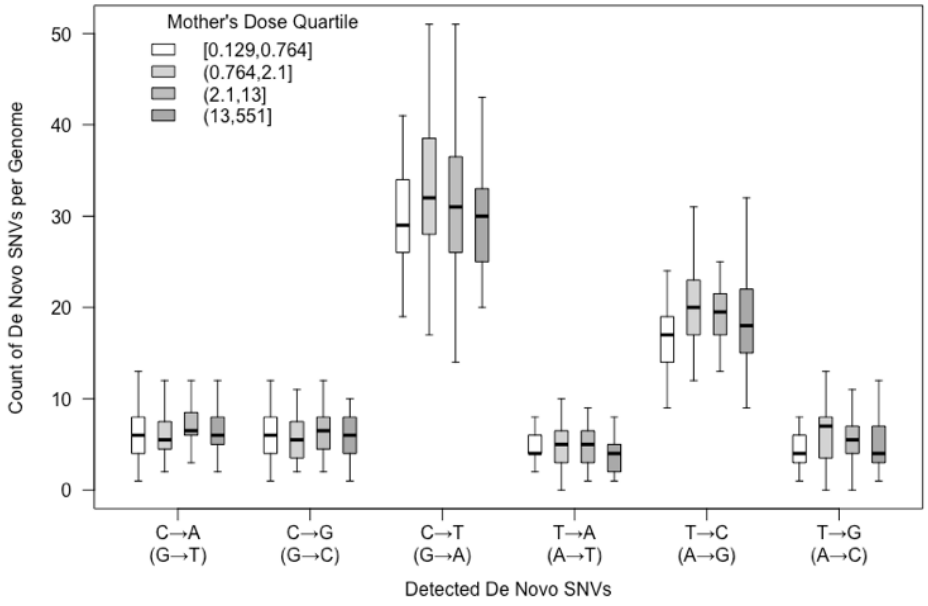


Figure S3. **De novo SNV signatures by preconception ionizing radiation dose**. The data are presented stratified by quartile of maternal preconception ionizing radiation dose and paternal preconception ionizing radiation dose.



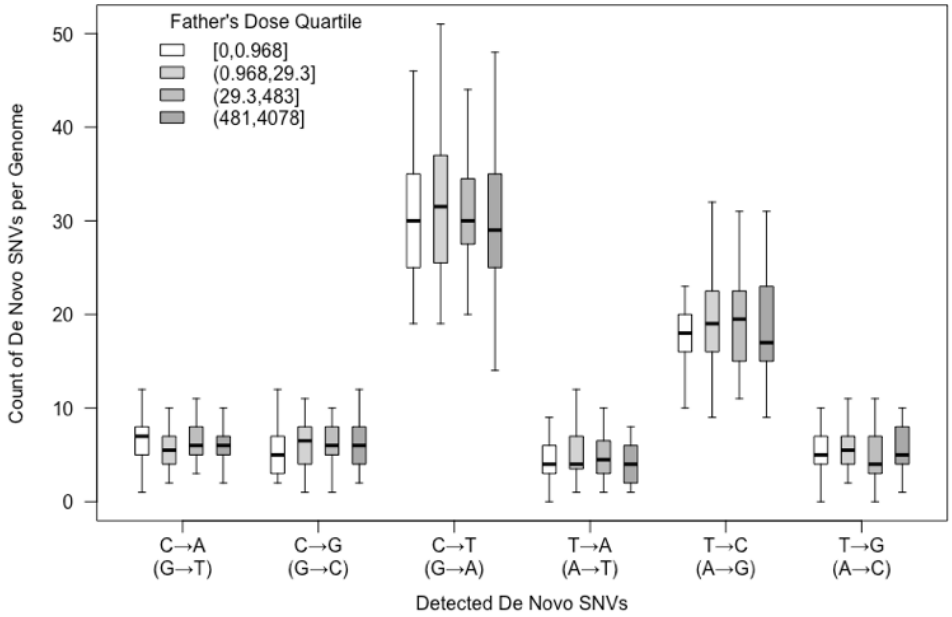
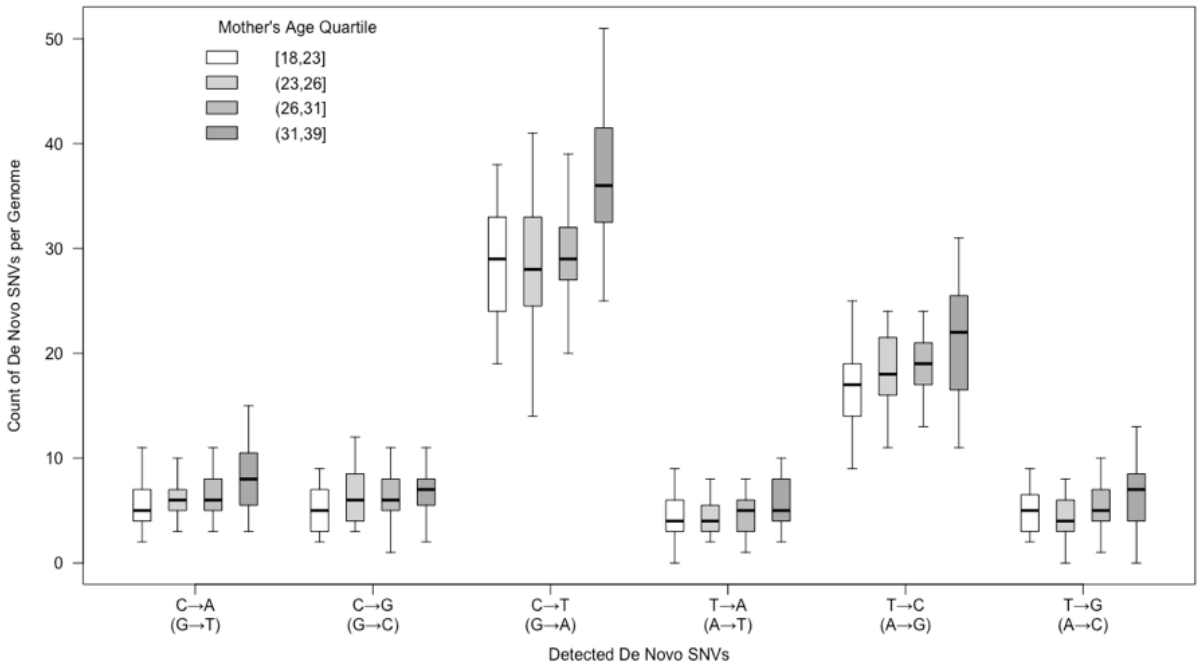


Figure S4. Distribution of de novo SNVs by quartiles of maternal and paternal age.



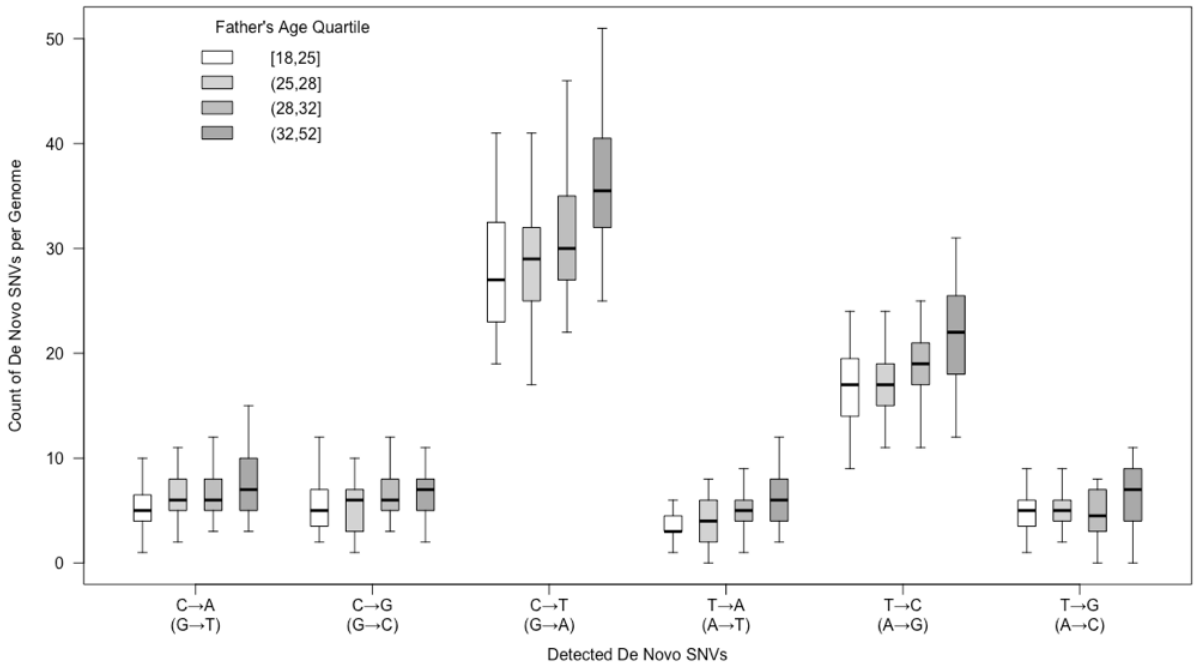


Figure S5. **Relationship between age at blood draw and qPCR measured relative leukocyte telomere length measured by qPCR in the collected Chernobyl trios**. Samples from children we collected between ages 15 and 30 (mean=24.28, median=24.67) and those from parents collected between ages 41 and 71 (mean=53.90, median=54.36). Symbols and colors denote males (blue) and female (red) samples. Gray line plots the overall relationship between age at blood draw and standardized T/S ratio.

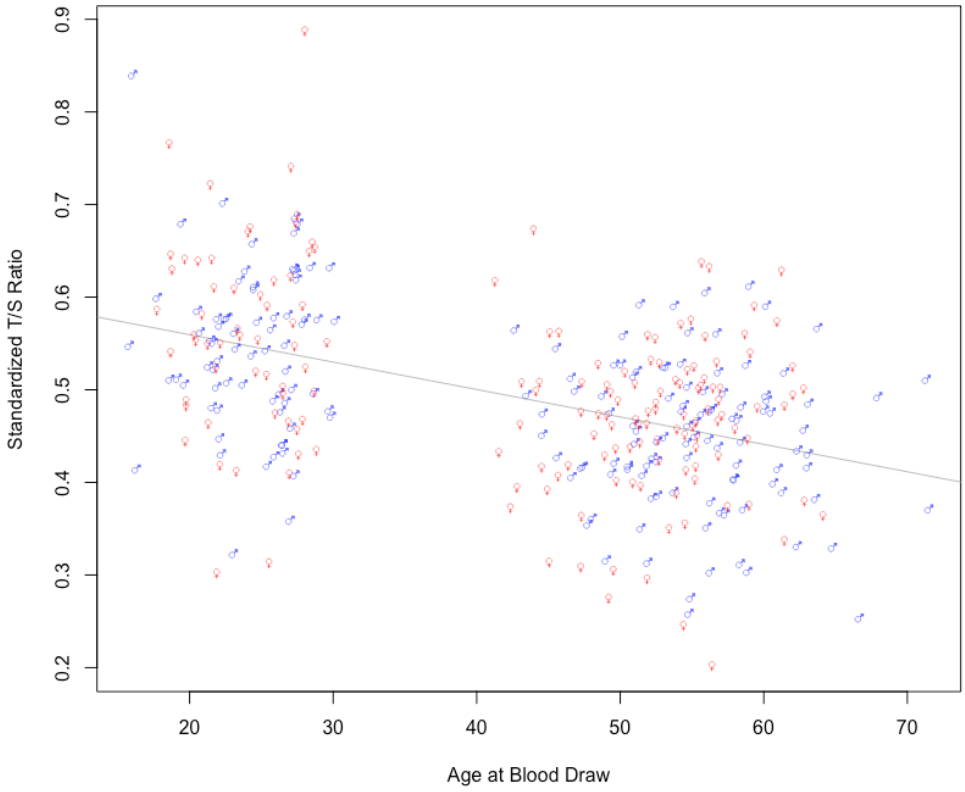


Figure S6. Schematic of DNM detection pipeline.

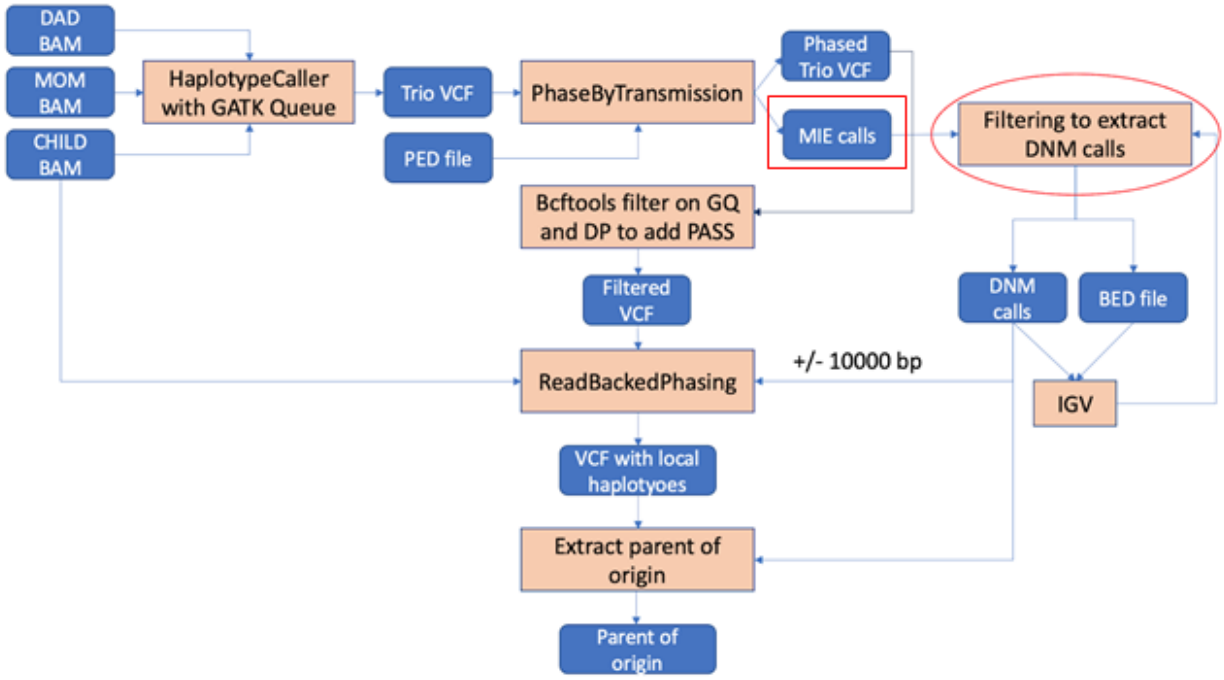
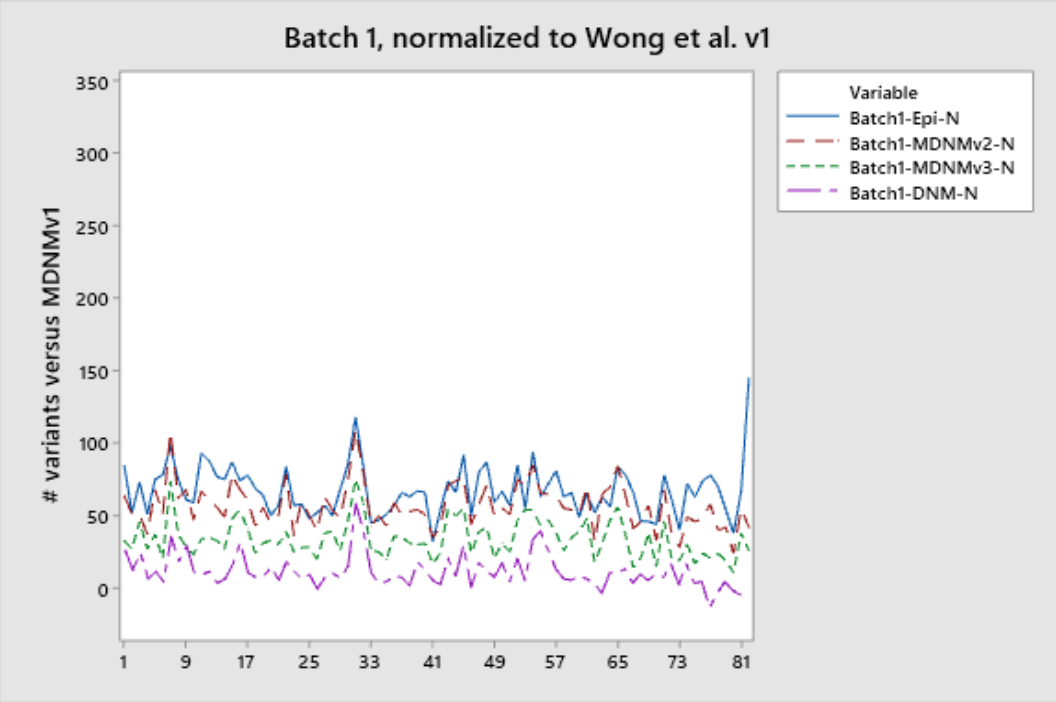
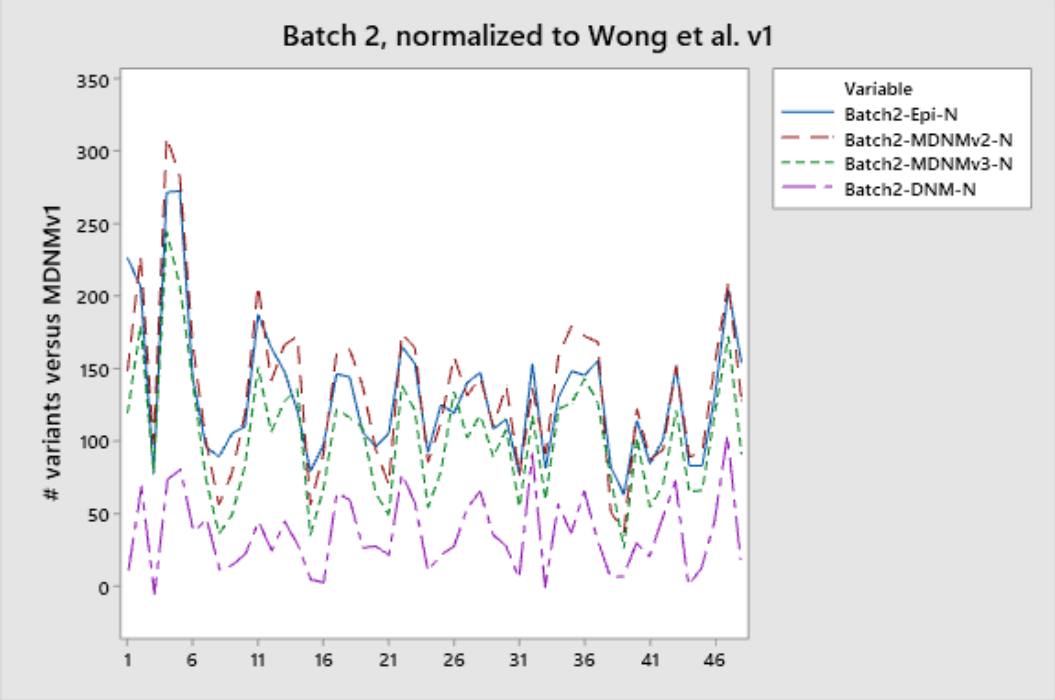


Figure S7. Performance of filtering strategies. Comparing the number of DNMs reported in the manuscript ("BatchX-DNM-N," pinkish-purple line), normalized to Wong et al. (*8*) results.





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