

BURDEN OF MALIGNANT MELANOMA IN UKRAINE IN 2002–2013: INCIDENCE, MORTALITY AND SURVIVAL

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Background: The malignant melanoma (MM) incidence rates were increasing and later stabilizing in many regions of the world, while in South-Eastern Europe incidence rates are uniformly increasing and mortality rates are higher. **Aim:** To describe burden of MM in Ukraine in terms of incidence, mortality and survival by sex, age and stage for the period 2002–2013 and compare with European countries. **Materials and Methods:** Database of the National Cancer Registry of Ukraine was used to extract MM incidence cases; number of MM deaths was obtained from the official mortality statistics. Age-standardised and age-specific incidence and mortality rates were calculated by sex, age groups (15–39, 40–59 and 60+); estimated annual percent of change was used to describe trends. Proportions of new cases by stage of disease and calendar period (2002–2007 vs 2008–2013) were compared as well as net survival estimates. **Results:** In Ukraine, MM was more common in females (age-standardised 5.3 per 100,000 in 2013; annual percent of change 3.5%) than in males (5.1 per 100,000; 4.1%); around 50% of them diagnosed in the age group 60+. The observed increase in proportion of new cases with early stage (I–II) was due to stage II cases. The slight increase in mortality rates in males or stability in females were not accompanied with increase of survival. Net MM survival was consistently lower comparing to European countries. **Conclusion:** More resources should be targeted to increase the capacity of healthcare in diagnostics and treatment of malignant melanoma, but also in promoting healthcare and education in Ukraine.

Key Words: malignant melanoma, incidence, mortality, survival, stage, cancer registry.

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The International Agency for Research on Cancer (Lyon, France) estimated 18.1 million new cancer cases and 9.6 million deaths from cancer worldwide in 2018. At the same time, the estimated number of new cases of malignant melanoma (MM) of skin and number of deaths from MM worldwide were 287,700 and 60,700 respectively [1]. The increase in MM incidence rates and their stabilization were observed in Australia, New Zealand, North America and Northern and Western Europe [2, 3], while in South-Eastern Europe incidence rates were uniformly increasing and mortality rates were higher [4]. In Ukraine, a lower-middle income country in Eastern Europe, in 2018 the estimated number of new MM cases was 3,853, or 2.4% of all newly diagnosed cases (excl. non-melanoma of skin cancer), and 1,389 deaths (1.4% of all cancer deaths) [5].

The well-established risk factors of melanoma are of geographical (e.g. latitude, intermittent sun exposure), biological (family history, numerous naevi, skin phototype, but also of socio-economic nature [6–9]. Ukraine is a lower-middle income country [10] in the Eastern Europe, geographic coordinates 49°00' N and 32°00' E, and has mostly temperate climate with the exception of the south-most coast of Crimea peninsula which has subtropical climate [11]. The average

temperature in summer is 18.8...20.8 °C with more than 290 sunny days in the year, the average UV (ultra violet) index in summer is 7–8 [12].

The National Cancer Registry of Ukraine (NCRU) was established in 1996 as a network of regional population-based cancer registries and achieved 100% population coverage in 2002. Using database of the NCRU, the critical source of information on the cancer burden in the country and ranked as a “high-quality registry” by the International Agency for Research on Cancer [13, 14] we aimed to describe burden of MM in Ukraine (incidence, mortality, survival) from 2002 to 2013 and compare with European countries.

MATERIAL AND METHODS

Data and sources. This is a population-based study of the MM cancer incidence, mortality and survival in Ukraine. A subset of 34,158 MM cases (13,750 males and 20,408 females) as defined by the code C43 of the International Classification of Diseases 10th revision [15] was extracted from the NCRU's database to assess incidence (cases diagnosed between 2002 and 2013) and survival. The quality of incidence data was evaluated elsewhere [13, 14, 16]. Mortality (2005–2013) and population figures (2002–2013) were obtained from the database of the State Statistics Service of Ukraine [17] and the Human Mortality Database [18] was used to obtain corresponding general mortality life tables for male and female population of Ukraine. We used number of MM deaths in 2002–2004 registered in the NCRU's database as of January, 1st 2020 because

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Abbreviations used: ASR – age-standardized rate; EAPC – estimated annual percentage change; MM – malignant melanoma; NCRU – National Cancer Registry of Ukraine.

unavailability of the number of MM deaths as it was reported within the broader group “deaths from all skin cancers”. Neither Clark, nor Breslow staging system is stored in the NCRU’s database, but TNM stage is a mandatory variable and was used in the present study. During the time period 2002–2011 stage of disease at diagnosis was coded according to the UICC’s TNM coding system guidelines, 4th edition [19], where applicable. Implementation of the 6th edition of the TNM started during 2012 in 21 out of 27 regional population-based cancer registries (77.8%). The closing date of follow up for survival estimates was 31th December 2018.

Statistical analysis. Overall age-standardized incidence and mortality rates (ASR) were calculated by the direct method alongside with truncated ASR calculated for “young” (age at diagnosis 15–39), “middle” (40–59) and “older” (60+) age groups for both males and females using Segi-Doll’s World population [20]. To evaluate incidence and mortality time trends we calculated estimated annual percent change (EAPC) of rates. Five-year net survival estimates were produced using Pohar–Perme method [21] stratified by sex, age-groups (15–39, 40–59, 60+) and period of diagnosis (2002–2007 vs 2008–2013) and net survival curves were compared [22] with the significance level set to 0.05. All calculations were performed using the R software, version 3.6.3 [23, 24].

RESULTS

In Ukraine, MM was more common in females (2,073 new cases, ASR 5.3 per 100,000 in 2013) than in males (1,488 new cases, ASR 5.1 per 100,000 respectively); around 50% of them diagnosed at age group 60+ (Table 1). The overall incidence rates increased significantly with EAPC 4.1% in males and 3.5% in females during the study period of 2002–2013 (Supplementary tables 1–2*). The highest increase was observed for the age group 60+ with EAPC 5.9% (males) and 5.0% (females), as well as in young females (15–39), where ASR increased from 1.9 per 100,000 in 2002 to 3.2 per 100,000 in 2013 (EAPC 4.3%). In the age groups 15–39 and 40–59, incidence rates were consistently higher in females, while in 60+ group female rates were on average 1.5 times lower (Fig. 1, Supplementary Table 2).

The overall mortality rates were increasing in males (ASR 1.6 to 1.8 per 100,000, EAPC 1.9%) and stable in females. Significant increase in mortality rates during 2002–2013 was observed in age group 60+ both in males and in females (EAPC 3.5% and 3.0% respectively). At the same time mortality rates in female age groups 15–39 and 40–59 were decreasing, significantly in case of latter group (EAPC –1.4%), while in males they were stable (Table 1, Fig. 1, Supplementary Tables 1–2).

Analysis of incidence by stage of disease and calendar period (Fig. 2) showed that the proportion of cases with early stage (I–II) was more than 50%

and has increased, but this increase was due to new stage II MM cases (by 5–7% in males and 8–9% in females) diagnosed in all age groups. The proportion of stage I cases in males was decreasing with age and period, while in females we observed it only in age group 60+ (n.s.). In all ages the proportion of late stage (III–IV) cases decreased in 2008–2013 comparing to 2002–2007 both in males (from 25.9% to 19.9%) and in females (21.3% to 16.1%). The proportion of cases with unknown stage was stable in two periods in each age group ranging from 11.6% to 15.5% in males and from 12.7% to 15.9% in females (Supplementary Table 3).

The overall net survival for females was consistently higher than that in males for both study periods (2002–2007 vs 2008–2013), 5-year net survival for cases diagnosed in 2008–2013 was 51.3% in males and 62.4% in females with no statistical difference between periods for both sexes (Table 2, Supplementary Table 4). Further comparison of the net survival proportions between two periods of diagnosis by stage showed statistically significant increase among males with stage I (from 69.3% for 2002–2007 to 71.5 for 2008–2013) and decrease among females with stage II (from 64.8% to 60.6% respectively). No significant difference was observed comparing survival by other stage groups for both sexes (Supplementary Table 4). Table 2 and Fig. 3 show results for the period 2008–2013. Female patients had better stage-specific survival comparing to males. Median survival time was over 25 (males) and 49 months (females) except stage IV (6 and 10 months respectively). Three- and five-year survival estimates in patients with unknown stage were similar to stage III rates. In females, the net survival estimates were statistically different for two periods by age group, while no statistical difference was observed for males (data not shown).

DISCUSSION

In Ukraine, overall incidence rates were higher in females, while mortality rates were higher in males. This differs from incidence and mortality patterns observed in Western and Northern Europe and South-Eastern Europe [3, 25]. In the former both incidence and mortality rates in females are higher, while in later incidence rates were higher in males. In our study, we observed increase in incidence rates of MM for both males and females during 2002–2013. Comparing to European countries [2, 3, 26, 27], lower or similar rates were reported for Portugal in 2005 (ASRs 2.4 per 100,000 in males and 3.8 in females), and for 2000–2002 in Bulgaria (ASRs 2.6 in males and 2.2 in females per 100,000), Belarus (ASRs 2.8 in males and 3.7 in females per 100,000) and the Baltic countries (Estonia, Latvia, Lithuania: 3.0–5.0 per 100,000 in males and 4.2–6.7 per 100,000 in females). In neighboring Slovakia, ASRs were 6.7 and 6.6 per 100,000 respectively and in the rest of European countries the incidence rates were even higher.

*Supplementary materials are available from http://ncru.inf.ua/data/MelPaper/melanoma_suppmaterials.docx.

Table 1. Incidence and mortality rates, estimated annual percent of change of malignant melanoma by sex and age, Ukraine, 2002–2013

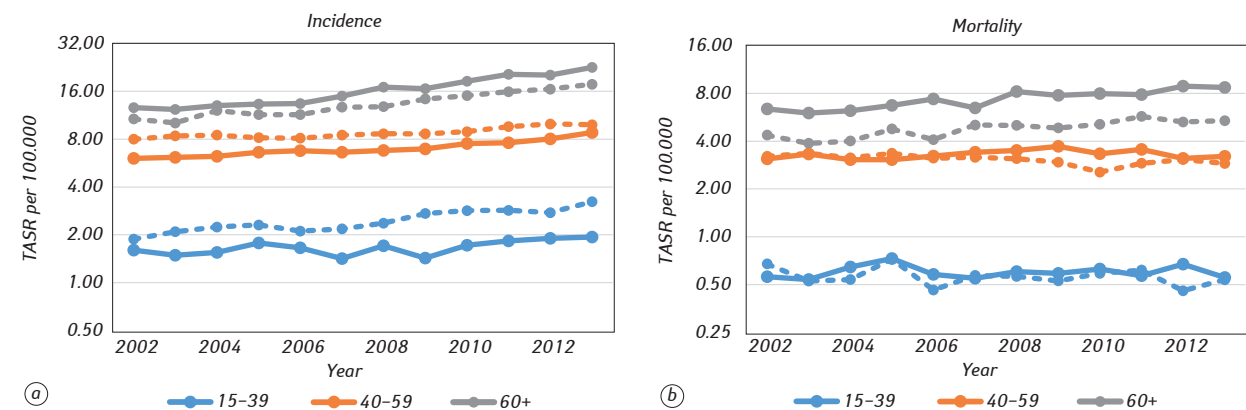
Sex	Incidence					EAPC, %†	Mortality				EAPC, %†
	Cases (%)		ASR*		Deaths (%)		ASR*				
	2002	2013	2002	2013	2002‡		2013	2002‡	2013		
Males											
15–39	147 (15.3)	178 (12.0)	1.6	1.9	1.8 (0.042)	52 (11.2)	55 (9.7)	0.6	0.6	0.1 (0.889)	
40–59	343 (35.8)	538 (36.2)	6.0	8.8	3.1 (< 0.001)	176 (37.8)	198 (35.0)	3.1	3.2	0.6 (0.267)	
60+	468 (48.8)	770 (51.7)	12.6	22.6	5.9 (< 0.001)	238 (51.1)	311 (55.0)	6.4	8.7	3.5 (< 0.001)	
All ages	959 (100)	1,488 (100)	3.3	5.1	4.1 (< 0.001)	466 (100)	565 (100)	1.6	1.8	1.9 (< 0.001)	
Females											
15–39	178 (12.4)	288 (13.9)	1.9	3.2	4.3 (< 0.001)	64 (11.0)	52 (8.6)	0.7	0.5	−1.2 (0.305)	
40–59	535 (37.4)	707 (34.1)	8.0	9.9	1.9 (< 0.001)	216 (37.0)	212 (35.0)	3.2	2.9	−1.4 (0.014)	
60+	713 (49.9)	1,073 (51.8)	10.7	17.7	5.0 (< 0.001)	303 (52.0)	341 (56.4)	4.4	5.4	3.0 (0.001)	
All ages	1,430 (100)	2,073 (100)	3.6	5.3	3.5 (< 0.001)	583 (100)	605 (100)	1.4	1.4	0.2 (0.584)	

Notes: *ASR – age standardized rate per 100,000 (using standard world population); †EAPC – estimated annual percent change, p-level in parentheses; **bold** indicates statistical significance (p < 0.05); ‡Registry's data.

Table 2. Net survival estimates and median survival time for cases diagnosed in 2008–2013, by sex and stage, malignant melanoma, Ukraine

Sex	Stage	Time							
		1-year		3-year		5-year		Median	
		Net survival	S.E.*	Net survival	S.E.*	Net survival	S.E.*	Months	95% CI†
Males	I	94.9	0.6	78.6	1.1	71.5	1.4	--	135–...
	II	89.9	0.8	63.1	1.3	52.8	1.5	66	60–75
	III	74.3	1.4	41.2	1.7	32.0	1.8	25	22–29
	IV	32.7	2.5	11.8	1.8	9.0	1.8	6	5–7
	Unknown	66.5	1.6	44.5	1.9	36.3	2.2	27	24–33
	Overall	82.9	0.5	59.6	0.7	51.3	0.8	67	61–74
Females	I	96.8	0.4	84.6	0.7	78.4	1.0	-	128–...
	II	93.6	0.5	71.6	1.0	60.6	1.2	93	81–115
	III	80.7	1.1	56.3	1.5	46.3	1.7	49	41–57
	IV	41.9	2.8	18.6	2.4	12.0	2.2	10	8–11
	Unknown	75.8	1.3	55.6	1.6	47.7	1.8	52	43–63
	Overall	89.1	0.3	70.8	0.5	62.4	0.6	174	149–...

Notes: *S.E. – standard error; †95% CI – confidence interval with confidence level 95%.

**Fig. 1.** Malignant melanoma incidence (a) and mortality (b) by sex and age, 2002–2013, Ukraine. Solid lines — males; dashed lines — females; TASR — truncated age-standardized rate per 100,000 (using world standard population)

Analysis by age at diagnosis showed that the highest increase in incidence rates was in age group “60 years and older”, in which truncated ASR increased by 80% (males) and 65% (females) over 12 years. We also noted an increase in incidence rates in young females of age 15–39 years at diagnosis with annual percent of change (EAPC) 4.3% and middle-aged males of age 40–59 years (EAPC 3.1%). These results are in line with obtained for Eastern Europe previously [2] and could be explained with the increase in sunbed use and change in holiday habits of Ukrainians (e.g. Egypt and Turkey as main places of summer vacations) during the study period. Although almost 60% of MM cases in males and 70% in females were diagnosed at early stage (I–II) and increased with time, the proportion of stage I cases decreased in all age groups and both sexes. The expected increase in awareness (e.g. annual “Melanoma Day” since 2009 [28]) does not seem to be enough and must be accompanied with increase

in availability of diagnostics and treatment and reduction of out-of-pocket payments [29].

The MM mortality rates were higher in males than in females during 2002–2013. Overall mortality rates were stable or slightly increasing, but remained one of the highest comparing to other Central and Eastern European countries [5, 25]. Analysis by age showed stability or decrease of rates in young and middle age groups in both sexes. The highest increase was observed in age group 60+ in both sexes (EAPC 3.5% in males and 3.0% in females). The same pattern was observed in the study of MM mortality rates in the South-Eastern European countries but for different age groups definition (25–49, 50–69, 70+) [4]. Despite large proportion of cases discovered in stage I and II, this has not reflected in decrease of mortality yet; however, this type of analysis could also benefit from assessing not only stage distributions but also the stage-specific incidence rates [30]. It has also

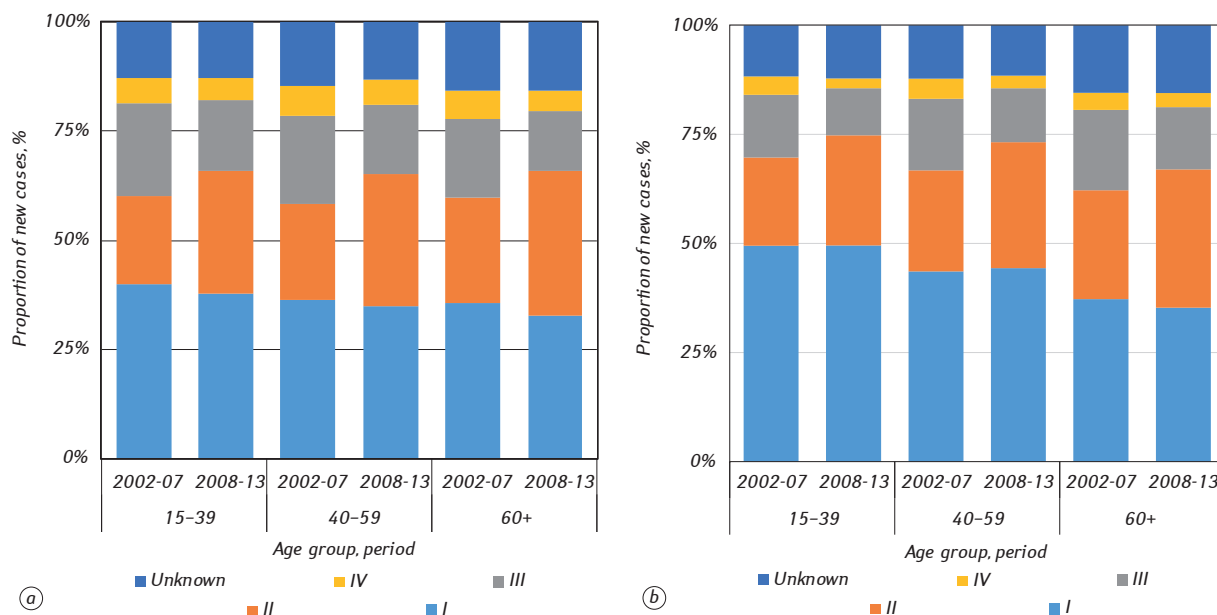


Fig. 2. Proportions of new cases of malignant melanoma by TNM stage, sex, age and period, 2002–2013, Ukraine, males (a), females (b)

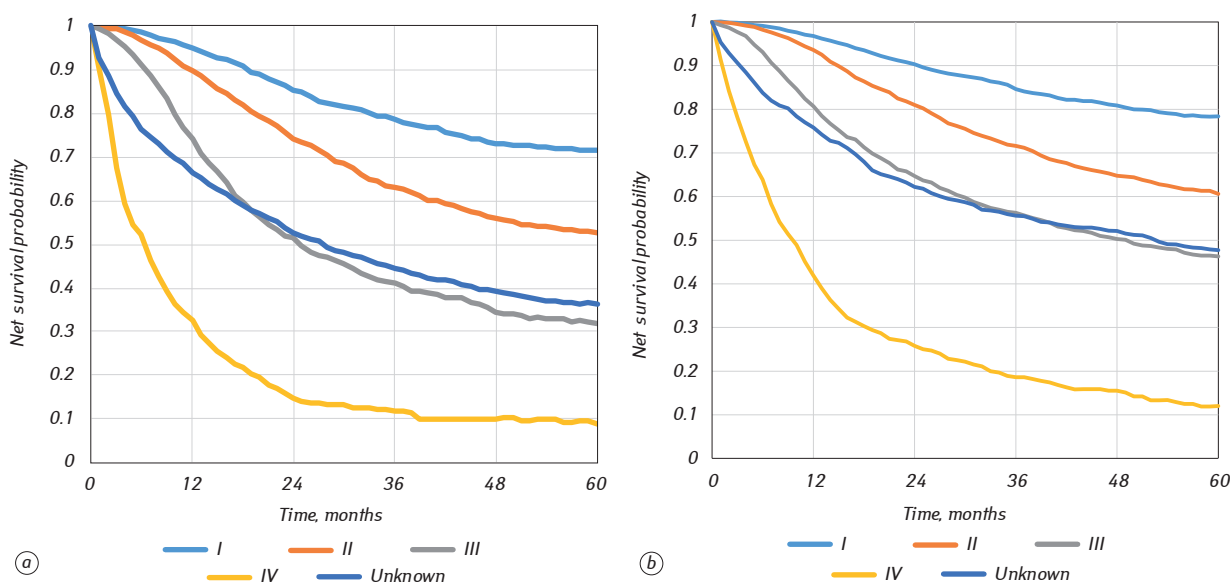


Fig. 3. Overall net survival for males (a) and females (b) with malignant melanoma diagnosed in 2008–2013 by stage, Ukraine

been shown the reliability of cancer death certificates might be lower in older age groups with tendency to overestimate cancer-specific mortality [31]; with the increasing incidence of MM observed in our study it is possible that this phenomenon might also be present in the mortality data.

A study on trends in survival in European countries showed that melanoma survival was increasing in 1990–2004 [32]. In a recent study (EUROCARE-5) of skin melanoma in Europe the age-standardized five-year relative (or net) survival ranged from 74.3% in Eastern Europe to 87.7% in Northern Europe for cases diagnosed in 2000–2007 (both sexes combined) [33]. In our study, the overall 5-year net survival estimates (similar to age-standardized ones as shown in Supplementary Table 5) increased for both males (51.3%) and females (62.4%) for cases diagnosed in 2008–2013 comparing to 2002–2007. Comparing to European countries these

estimates were lower except for Bulgaria (49.6%). One of the explanation of poor survival is due to late stage diagnosis, but survival rates for stage I cases were lower comparing to USA, where the five-year relative survival (without age standardization) is 92% and for primary melanoma without lymph node involvement 98% [34]. This difference could be explained by three reasons: 1) misclassification caused due to transfer from 4th to 6th edition of the TNM classification and AJCC staging that are still used in Ukraine; 2) delays in treatment due to healthcare specifics system (e.g. dermatologists perform diagnostic procedures, while specialized treatment can be provided only in oncological clinics); 3) limited access to innovative medicines for metastatic melanoma, inequalities in access to diagnostics and treatment.

Among limitations of the study is the unavailability of complete data for the period 2014 onward due

to drop in population coverage by the NCRU because of Crimea occupation and major anti-government activities in the eastern part of the country. These unfavorable events resulted in the drop of population coverage by cancer registration to approximately 85% [35] and absence of precise and accurate person-year numbers for the temporary occupied regions. We observed (data not shown) decrease in total number of new MM cases in 2014 by 976 (401 in males and 575 in females) compared to 2013; ASR in males decreased from 5.1 to 4.6 per 100,000 in males and from 5.3 to 4.7 per 100,000 in females. During next five years ASRs increased to 5.0 (in males, EAPC 2.0%) and 4.9 (in females, EAPC 1.9%) per 100,000 in 2018 [36]. As to mortality, decrease in number of recorded MM deaths by 175 in both sexes did not change the value and trend of ASRs in females, while rates in males increased from 1.8 to 2.1 per 100,000 on average [17].

Less than 15 years of observation prohibited studying cohort effects [37]. The main strength of the study is that population-based cancer registry's data of sufficient quality was used for incidence and survival estimates. This study presents results for Ukraine, second largest country in Europe, but also representing its Eastern part, where historically less information on cancer burden available [3]. Availability of stage in the NCRU's database is also among the strengths of the study.

CONCLUSIONS

The incidence rates of MM in Ukraine increased both in males and in females during 2002–2013 (EAPC 4.1% and 3.5% respectively), especially in age group of 60 and older. Slight increase of MM mortality rates in males (1.9%) and their stability in females (0.2%) were not accompanied by increase in survival rates. The five-year net survival estimates were lower comparing to USA and European countries even for cases diagnosed with stage I of disease. More resources should be targeted to increase the capacity of healthcare in diagnostics and treatment of MM, but also in promoting healthcare and education in Ukraine. The transformation from the Semashko model of health care, known for its hierarchical organizational structure, central budgetary financing, no or not effective solutions in the financing of medical services and dominance of public sector [29, 38], to a new approach to the financing of healthcare institutions and practitioners, started in 2014 with the next step in 2020 focusing on secondary level is a good opportunity for these changes.

CONFLICTS OF INTEREST

None declared.

ETHICAL APPROVAL

Not required.

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