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Updated ENIGMA recommendations for reporting germline variants in cancer susceptibility genes and their translation into twenty languages

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For 'Presented at statement' see end of article.

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ABSTRACT

Genetic testing for cancer susceptibility underpins precision cancer prevention and care. Gaps in the healthcare providers' genetic literacy and an ambiguous lexicon for variant description may hinder proper delivery and clinical application of consistently trustworthy test results. The Evidence-based Network for the Interpretation of Germline Mutant Alleles (ENIGMA) international consortium supports controlled terminology and recommends a framework for reporting germline variants in cancer susceptibility genes, using breast cancer as an exemplar. Moving forward towards terminological coherence across disciplines and borders, the ENIGMA Clinical Working Group launched a multinational effort to release consortium-approved translations of the published recommendations. The herein reported Vocabulary Translation Project offered an opportunity to reappraise and align the reference text to the recent *BRCA1* and *BRCA2* specifications to the American College of Medical Genetics and Genomics/Association for Molecular Pathology rules by the ENIGMA Variant Curation Expert Panel and to highlight country-specific differences in breast cancer risk assessment and management. The updated

WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ Genetic testing for cancer predisposition serves as a precision medicine tool, requiring unambiguous interpretation and communication of test-derived information.
- ⇒ Inconsistency in the lexicon used to capture the consequences of germline gene variants is a concerning issue among languages and may lead to incorrect clinical inferences and decisions.

WHAT THIS STUDY ADDS

- ⇒ As a step forward towards consolidated terminology for reporting germline variants in cancer susceptibility genes, we now provide updated recommendations to the Evidence-based Network for the Interpretation of Germline Mutant Alleles framework published in 2019, along with consortium-endorsed translations into 20 languages.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- ⇒ Supplied as easy to use documents, our recommendations cover 11 of the most widely spoken languages in the world, potentially benefitting a broad audience.
- ⇒ Standardised reporting of germline genetic test results will facilitate understanding among professionals across disciplines and borders and assist communication between providers and patients and their family members, supporting optimum choices for a more coherent and equitable clinical management of cancer risk.

recommendations and their 20 translations are now provided as easy to handle documents, covering 11 of the most widely spoken languages in the world. They will contribute to minimised erroneous inferences, more informed decision-making, improved health outcomes and equity in the use of genetic testing for cancer predisposition and in translational oncology.

Precision cancer prevention and care is a rapidly growing discipline in the field of medicine.¹ In the last decade, genetic testing for cancer susceptibility in high-risk individuals (and families) has been implemented in many countries worldwide. The advent and widespread application of massively parallel sequencing technologies, including multigene panels,² has further contributed to large-scale DNA testing for cancer diagnosis, treatment and risk prediction. Notably, cancer is a heterogeneous disease, characterised by a complex genetic architecture encompassing both somatic and germline (constitutional) variants; for breast cancer, the latter were categorised based on the level of their associated (high, moderate or low) cancer risks.³ Nevertheless, the terminology employed to describe these germline variants largely derives from a lexicon that is traditionally used for genetic diseases with classical Mendelian inheritance. This often leads to major communication hurdles among the differently specialised healthcare professionals, who are involved in the identification, counselling and clinical management of at-risk individuals, and it can make the conversation between providers and carriers of disease-associated variants challenging.

To address this issue, the Evidence-based Network for the Interpretation of Germline Mutant Alleles (ENIGMA) international consortium (<https://enigmaconsortium.org/>) published a position statement that included recommendations on how to report variants in cancer predisposition genes, focusing on breast cancer.⁴ The effort was prompted by the ENIGMA members' awareness that the terms used to report gene variants may have different meanings in multiple contexts and may be used interchangeably, with potential for erroneous inferences and thus inappropriate clinical interventions (see supplemental table 1 in ⁴). Incorrect interpretation of the clinical actionability of sequence variants can lead to their improper use as risk biomarkers to guide clinical decision-making and risk-reduction measures.^{5,6} A critical issue pertains to bioinformatic prediction tools, which often describe the effect of sequence variants on protein function using the very same terms that are employed to define the association of variants with cancer risk.^{4,7}

The recommendations included in the ENIGMA position article were compiled and published in English.⁴ However, as acknowledged by the compilers themselves, identical problems of misinterpretation and miscommunication occur also in other

languages. As a step forward towards consolidated terminology for variant reporting, and to avoid further heterogeneity (and potential misunderstandings) caused by non-rigorous translations of the proposed English lexicon, the ENIGMA Clinical Working Group launched an initiative aimed at translating the published recommendations into the various languages spoken by the international membership. First developed into an ENIGMA study concept in 2020, the Vocabulary Translation Project evolved over time in its scope to accommodate an increasingly important update and alignment step (as described below), reaching its full maturity and final shape in 2024.

We established 20 teams covering the languages listed in [box 1](#). All teams but one (see [box 1](#) footnote for specifics) included three to four individuals with expertise in clinical and/or molecular genetics. In total, 70 clinicians and researchers, based in 25 countries across four continents at the time of the translation, participated in the project.

As a first step, through collegial discussions and electronic surveys, we reached a majority consensus on the sections of the original position article⁴ that warranted translation. We aimed at a concise, easy to handle document, which eventually included: (a) a glossary of terms and general recommendations for describing and reporting variants in cancer predisposition genes; (b) the International Agency for Research on Cancer (IARC)⁸ and American College of Medical Genetics and Genomics/Association for Molecular Pathology (ACMG/AMP)⁹ five-tier schemes for disease gene variant classification; (c) the recommended terminology and descriptors for five-tier disease gene variant classification, considering variant pathogenicity in the multigene panel testing era and (d) suggestions for multitier reporting of cancer gene variants conferring high or moderate disease risk. We collated (a) based on excerpted passages and we derived sections (b)–(d) from tables 2–4 of the source article.⁴

Box 1 Languages covered by the Vocabulary Translation Project

List of available translations

Catalan (Català)
Chinese (中文)
Czech (Čeština)
Danish (Dansk)
Dutch (Nederlands)
Filipino (Filipino-Tagalog)
Finnish (suomi)
French (Français)
Galician (Galego)
German (Deutsch)
Greek (Ελληνικά)
Italian (Italiano)
Japanese (日本語)
Malay (Melayu)
Norwegian (Norsk)
Polish (Polski)
Portuguese (Português)*
Spanish (Español)
Swedish (Svenska)
Tamil (தமிழ்)

*Per their specific request, a fifth member was allowed in the initial Portuguese team for better addressing the differences between the Portuguese language spoken in Portugal versus in Brazil.

At the time of the original publication, ENIGMA served as an external panel for Clinical Genome Resource (ClinGen, <https://clinicalgenome.org/>), providing classifications based on the original in-house ENIGMA quantitative and qualitative criteria, which followed the IARC terminology and class assignment⁸ (<https://enigmaconsortium.org/enigma-classification-criteria/>, ENIGMA rules v.2.5.1 29 June 2017). ENIGMA has, since, sought and received approval as a Food and Drug Administration-aligned ClinGen internal Variant Curation Expert Panel (VCEP) for *BRCA1* and *BRCA2*. The VCEP now follows ClinGen ACMG/AMP guidelines and it has released *BRCA1* and *BRCA2* specifications to the ACMG/AMP rules (<https://cspec.genome.network/cspec/ui/svi/affiliation/50087>), available in the ClinGen Criteria Specification Registry. We used the opportunity of this translation

work to update the excerpts from the published recommendations⁴ and ensure their alignment with the current ClinGen-approved variant classification framework.¹⁰

The 20 teams worked independently on the assigned tasks via a two-step process, namely translation followed by back-translation—the latter serving as a verification step, by team members who were not involved in the translation, to confirm proper rendition of the original text/concepts. Our choice to opt for a so-structured, non-automated translation exercise proved useful to highlight concepts and sections that were particularly challenging, transversely across languages or in a language-specific manner, and it offered an invaluable opportunity for lively discussions, and for reappraisal and improvement of the reference text.

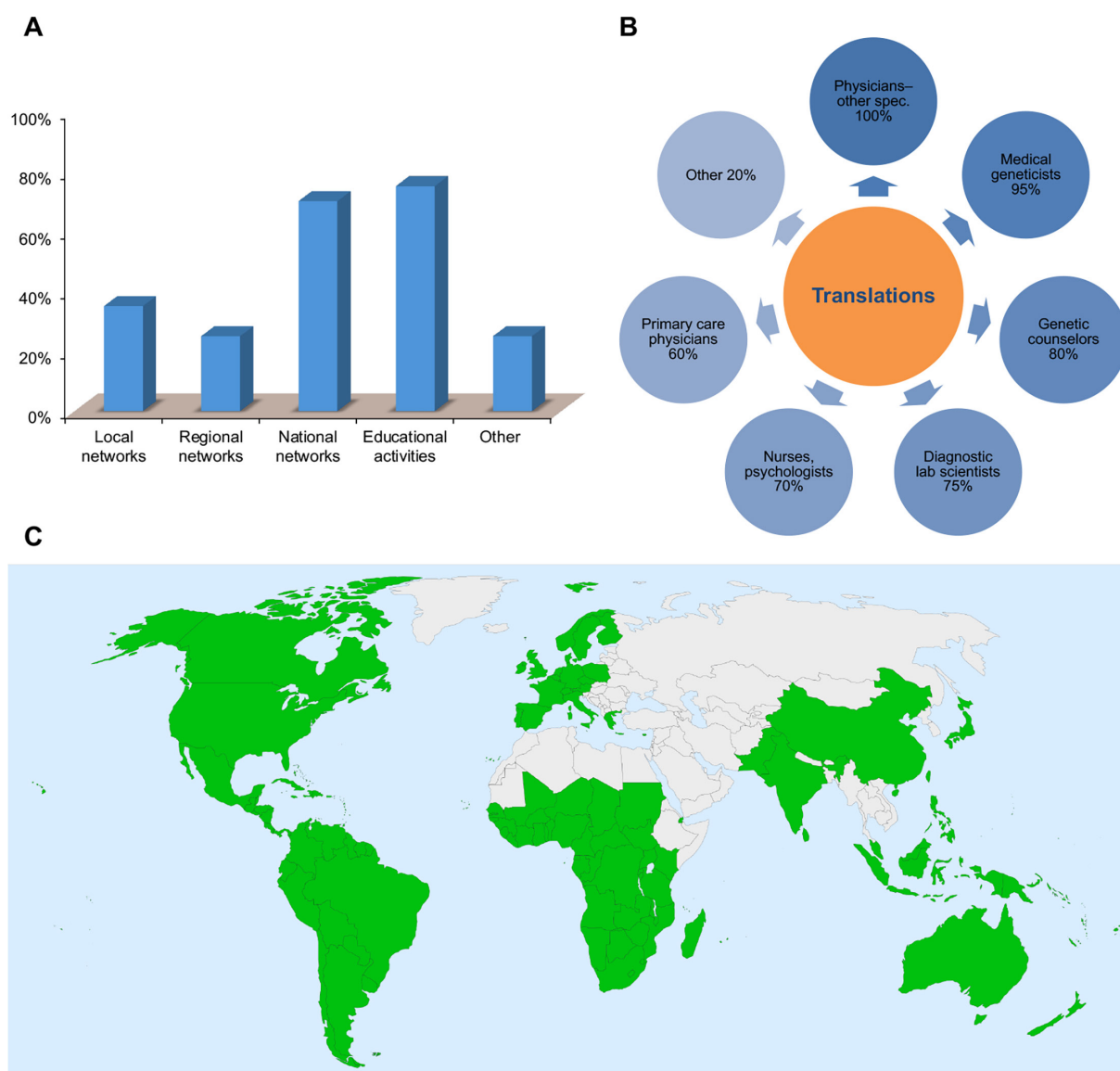


Figure 1 Vocabulary Translation Project: outreach strategies, target audience and potential reach. (A, B) Graphic summaries of the feedback collected via electronic surveys. (A) Most teams plan to disseminate the translated recommendations through educational programmes and activities and via national networks. Other modes include public health initiatives and (social) media. (B) The top professional category of intended users is represented by physicians—other specialties, encompassing medical oncologists, surgeons, pathologists, radiologists, radiotherapists, gynaecologists, gastroenterologists and any other specialists serving in multidisciplinary teams. Other includes journalists and science communicators, professionals from the pharmaceutical industry, government stakeholders, epidemiologists and bioinformaticians. (C) Countries and territories where English and the other 20 languages covered by our project are (co)official are highlighted in green. Note that because only entire countries and territories could be coloured, specific circumstances are not discernible. The map is for illustrative purposes only and not intended to represent the actual geopolitical situation. Software: Affinity Photo V.2.

Specifically, trans-national issues prompted revision of the excerpts to emphasise that the original article used breast cancer as an exemplar, with thresholds of risk categories derived from Easton *et al.*¹¹ and actionability per National Institute for Health and Care Excellence (NICE) guidelines-based risk stratification (<https://www.nice.org.uk/Guidance/CG164>)—we note that the NICE guidelines were chosen as a model because they explicitly link (cancer) risk to clinical action, helping to illustrate the importance of clarity about risk when genetic variants are interpreted and reported. This clarification was deemed necessary considering that breast cancer risk stratification cut-offs and management may vary depending on the guidelines used. Moreover, for other cancer types, the same relative risk may entail different actionability, depending on the absolute risk and the severity of the disease. Furthermore, we now specify (online supplemental appendix 1, glossary) that the terms *risk* and *penetrance* were used interchangeably in the reporting template of the original publication. We also point out that the terms *penetrant/penetrance* are preferred to indicate the probability of disease occurrence when reporting cancer predisposing variants in isolation, that is, when additional factors that contribute to cancer risk (other than gender and age) are not accounted for.

Country-specific differences in breast cancer risk assessment (eg, different absolute/relative breast cancer risk cut points) and management were noted by the translators. Moreover, even though we asked that the translated text be otherwise as faithful as possible to the reference source, certain concepts required language-specific elaboration for proper rendition, and, occasionally, sentences were rephrased or words inserted to underscore the translational slant of the effort. Any such adjustment(s), when considered major, were also marked as notes of the translators.

Online supplemental appendix 1 includes a glossary of terms and tables from the published article selected for translation, with amendments and corrigenda to the original English text made to comply with the current recommendations¹⁰ and to address any issues that emerged during the translation process. All 20 translations, available as online supplemental 20 translations, reflect this revised version of the reference source. Online supplemental appendix 2 provides details about the 20 language-specific teams.

On completion of the translation process, via electronic survey, we asked the participating teams to elaborate on the perceived significance and anticipated clinical utility of the translations. Overall, the feedback we collated recognises a high value of the translated recommendations for the wide medical community and for patients, and an expected positive impact on more consistent clinical management of carrier individuals, regardless of the English proficiency of the local, scientific or general, population.

We used multiple-choice questions to inquire about the outreach strategies (How do you plan to use/promote the use of the translation in your country?) and the target audience (Whom do you envision as the ideal target audience/users of this translation in your country?). The delineated outreach programmes include the use of the translations for education and training purposes (75%), as well as dissemination via local (ie, institutional, including websites), regional and especially national (eg, scientific societies, consortia, working groups) networks (35%, 25% and 70%, respectively) (figure 1A). The identified target audience encompasses primarily physicians of other specialties who participate in multidisciplinary teams, but also medical geneticists, genetic counsellors and other professionals involved in the counselling process, primary care physicians, members of

diagnostic laboratories, as well as non-healthcare professionals, for example, journalists and science communicators (figure 1B).

Fostered terminological coherence will be especially relevant to health professionals who might not be well acquainted with cancer genetics and/or work in community settings.^{12 13} It will also facilitate mutual understanding and exchange among providers from different disciplines and help individuals who carry variants in cancer susceptibility genes to gain clearer knowledge of the risks and clinical consequences associated with their status and to appreciate the value of report updating.¹⁴ This will, in turn, guide tested individuals and their blood relatives towards more appropriate choices and ensure better adherence to (national or international) guidelines.¹³

Pitfalls in sequence variant interpretation and communication have been reported as a potential cause of incorrect or missed diagnoses, unnecessary treatments and interventions, heightened anxiety and distress for patients and family members.¹³ Ideally, in countries where English is not the official language used for written and/or verbal communication with patients, the documents herein presented could improve reporting of test results on cancer predisposition. This would ultimately lead to more consistent translation of genetic testing findings into the most clinically appropriate cancer prevention and care.

Considering the estimated ~2.2 billion native speakers of the 20 languages covered by this project, along with the recorded ~400 million English native speakers (Ethnologue, <https://www.ethnologue.com>, editions 22–24), the updated ENIGMA recommendations for reporting germline variants in cancer susceptibility genes and their translations could altogether benefit a wide audience of about one third of the current ~8.2 billion global population (United Nations, World Population Prospects, <https://population.un.org/wpp/>). Moreover, because our collection covers 11 of the 45 most widely spoken languages in the world (Ethnologue, edition 25), including English, Spanish, French and Portuguese, which are (co)official languages in a number of countries and territories, the reach of this project may extend to an even greater proportion of the world population (figure 1C).

By overcoming the language barriers across disciplines and countries, the translated controlled vocabulary and framework are provided here to advance towards more equity in the use of genetic testing for cancer predisposition and in (access to) translational oncology and precision medicine. We hope that harmonised communication of germline genetic test results will contribute to reduced misdiagnoses and to more coherent clinical management, eventually improving health outcomes. In keeping with the original report, the updated recommendations and their translations are not intended to provide guidance for clinical treatments. The latter remains an oncologist's decision, which our documents may assist by ensuring correct reporting of the detected variants and associated risks.

As previously stated,⁴ because knowledge of the genetic bases of cancer predisposition is constantly evolving, and so is the related lexicon used for description, we predict that our recommendations (and their translations) will require periodic revision and amendment. In this regard, the use of 'atypical penetrance' is currently under consideration for a more general description of any variant displaying disease penetrance features that may be actionable, yet distinct from those of average pathogenic variants in that disease gene (eg, as described in references^{15 16}).

We used breast cancer as a blueprint. Future iterations of this exercise might extend to include other cancer types, on proper calibration of the cancer-specific absolute and relative risks. The latter direction, along with a focus on the evolving terminology and communication issues related to the interpretation

and actionability of reduced penetrance variants, aligns with the mission of the ENIGMA Clinical Working Group and will be pursued under its umbrella. Because we expect that the ENIGMA consortium membership, which currently comprises 221 officially enrolled affiliates from 37 countries (as of 31 December 2025), will continue to expand, it is likely and desirable that an exercise like ours will encompass additional languages in the future.

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The study, in its current shape, was presented as an abstract at the Tenth International Symposium on Hereditary Breast and Ovarian Cancer in 2025 (Fam Cancer 2025;24:80).

Correction notice This article has been corrected since it was published. The open access license, CC BY NC, has been added of 17th July 2026.

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Contributors ADN and PR conceived and implemented the study as presented in this final form. ADN, DME, ABS and PR identified excerpts from the original article for critical review and consensus by the other authors and aligned the text to the current variant classification framework. All authors but DME and ABS worked on their translations. ADN supervised the work of the 20 teams providing overall guidance. ADN and PR designed the electronic surveys. All authors but ADN, DME, ABS and PR participated in the surveys. ADN collated the results and worked on graphic summaries. ADN and PR drafted the manuscript. ADN, DME, ABS and PR edited the draft with input from the other authors. All authors approved the final manuscript. ADN is the guarantor.

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