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Position statement from the Italian Society of Human Genetics (SIGU) on the implementation of germline pharmacogenetic testing

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The Italian Society of Human Genetics (SIGU) Working Group on Pharmacogenomics has released recommendations for the implementation, interpretation and reporting of germline pharmacogenetic testing in clinical practice within the Italian National Health Service (SSN). These guidelines outline the key principles for the responsible use, reporting, and interpretation of pharmacogenetic data, emphasizing clinical validity, clinical utility, cost-effectiveness, and ethical considerations. With the aim of promoting a systematic standardized, and evidence-based implementation of germline pharmacogenetic testing in Italy, SIGU strongly recommends addressing the following points: (1) Pharmacogenetic testing should be performed based on validated scientific evidence, primarily following Association for Molecular Pathology (AMP) and Dutch Pharmacogenetics Working Group (DPWG) guidelines, and restricted to gene–drug pairs with ClinPGx clinical annotation level 1 A. (2) Patients must be appropriately informed and provide specific consent, particularly when pharmacogenetic data are derived as secondary findings from diagnostic next generation sequencing (NGS) analyses. (3) Testing should prioritize clinically actionable variants that influence therapeutic efficacy or prevent severe adverse drug reactions. (4) The interpretation and reporting of results must be carried out by a qualified geneticist in collaboration with clinical pharmacologists to ensure appropriate therapeutic recommendations. (5) The implementation of pharmacogenetic testing should be supported by robust quality assurance procedures in laboratories, in line with international standards. (6) The inclusion of pharmacogenetic tests in the Italian LEA (Essential Levels of Assistance) should be updated in accordance with international evidence and EMA-AIFA recommendations. (7) Further pharmaco-economic and psychosocial research is needed to evaluate the impact of pre-emptive versus reactive testing strategies on patient outcomes and healthcare sustainability.

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INTRODUCTION

In October 2025, the Italian Society of Human Genetics (Società Italiana di Genetica Umana, SIGU) issued the first national recommendations on good practices for the execution and reporting of germline pharmacogenetic testing [1]. The document, produced by the SIGU Working Group on Pharmacogenomics and approved by the SIGU Executive Committee, represents a major milestone in the clinical implementation of pharmacogenetics within the Italian National Health Service (Servizio Sanitario Nazionale, SSN). It aims to harmonize testing strategies, ensure methodological quality, and promote equitable access to clinically relevant pharmacogenetic analyses.

Over the past decade, the field of pharmacogenomics has undergone rapid development, driven by technological advances in next-generation sequencing (NGS) and by increasing awareness of genetic variability as a determinant of drug response [2]. These advances have brought to light a large body of evidence demonstrating that germline variants in pharmacogenes can significantly alter therapeutic efficacy and determine toxicity by influencing pharmacokinetics (e.g., Cytochrome P450 enzymes affecting drug metabolism), as well as pharmacodynamics (e.g., VKORC1 variants affecting drug response), or causing hypersensitivity reactions (e.g., HLA alleles associated with idiosyncratic adverse events).

Despite this, the implementation of germline pharmacogenetics within national healthcare systems has been uneven across Europe, often limited by the absence of consistent regulatory frameworks and by heterogeneous reimbursement policies [3].

In Italy, the clinical implementation of germline pharmacogenetic testing remains fragmented, inconsistently regulated, and variably

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Table 1. germline pharmacogenetic tests currently reimbursed within the Italian LEA framework and related critical issues.

Gene (germline)	Drug	Clinical indication/context	Critical issues
CYP2D6	Gefitinib	Non–small cell lung cancer (NSCLC)	No established germline pharmacogenetic rationale for CYP2D6–gefitinib. Mandatory testing in this setting concerns **somatic EGFR mutations**, not germline pharmacogenetics.
CYP2C19	Erlotinib	Non–small cell lung cancer (NSCLC)	Erlotinib is not a CYP2C19 substrate. Mandatory **EGFR tumor testing** is somatic
UGT1A1	Atazanavir	HIV infection – risk of unconjugated hyperbilirubinemia	UGT1A1 testing is reimbursed for atazanavir-associated hyperbilirubinemia, while **UGT1A1 testing for irinotecan toxicity**, supported by EMA recommendations and high-level evidence, is not included in LEA.

This table describes the current Italian LEA reimbursement framework for germline pharmacogenetic testing. The listed examples do not represent SIGU recommendations and highlight regulatory inconsistencies and historical classifications that are not aligned with contemporary pharmacogenetic evidence or international guidelines. One of the main aims of this document is precisely to propose the inclusion in the LEA of correct drug-gene pairs, supported by international scientific evidence.

reimbursed. The inclusion of genetic tests within the Italian National Health Service (Servizio Sanitario Nazionale, SSN) is governed by the *Livelli Essenziali di Assistenza* (LEA) — the "Essential Levels of Care", a national list of the healthcare services that must be uniformly provided across all Italian regions and are partially or fully reimbursed for all citizens. Despite growing international evidence supporting the clinical utility of pharmacogenetic testing, the current LEA framework (updated in January 2025) includes only three germline pharmacogenetic tests: *CYP2D6*, *CYP2C19*, and *UGT1A1* genotyping (Table 1). Moreover, their reimbursement is restricted to highly specific drug indications — *gefitinib*, *atazanavir*, and *erlotinib*, respectively — without clearly defining the underlying clinical indication or the pharmacogenetic rationale. Importantly, for *gefitinib* and *erlotinib*, mandatory testing in clinical practice concerns somatic *EGFR* mutations, rather than germline pharmacogenetic variants. Tests of proven clinical value are notably absent from current LEA, such as *DPYD* genotyping (recommended by AIFA since 2020 for fluoropyrimidine therapy), *CYP2C9* testing before *siponimod* treatment, *UGT1A1* for *irinotecan*, *TPMT* for *thiopurines*, and *CYP2C19* for *mavacamten*. It should be emphasized that the *drug-gene pairs* listed in Table 1 do not reflect SIGU recommendations, but rather describe the current LEA reimbursement framework, which in some cases is based on historical or regulatory classifications that are not supported by contemporary pharmacogenetic evidence.

This limited and outdated inclusion leads to inequitable patient access and potential safety gaps, as many pharmacogenetic tests endorsed by EMA, AIFA, and international consortia (AMP, DPWG, CPIC) are not reimbursed under the SSN. Moreover, authorities in each Italian region are acting independently in how they implement and supplement the nationally defined LEAs, with little coordination among regions. As a result, the way LEAs are applied varies widely from region to region and is often shaped by the differing economic resources and priorities of each regional health system. Hence, clinicians and laboratories in Italy are facing uncertainty regarding test appropriateness, and many analyses are either performed privately or omitted altogether. From an economic standpoint, this omission is paradoxical: adverse drug reactions (ADRs) account for a significant proportion of hospitalizations and healthcare costs [4].

The SIGU Working Group therefore, highlights the urgent need to update the LEA to include pharmacogenetic tests supported by high-level evidence (ClinPGx level 1 A) and endorsed by AIFA/EMA, thereby ensuring equitable access, patient safety, and more efficient use of healthcare resources.

At present, the only nationally recognized Italian guidelines specifically addressing pharmacogenetic testing in clinical practice are those jointly developed by the Italian Society of Pharmacology (SIF) and the Italian Association of Medical Oncology (AIOM), which provide recommendations for the use of pharmacogenetic analyses in oncology to optimize specific therapies -- such as fluoropyrimidines and *irinotecan*, -- and prevent severe adverse drug reactions [5].

The SIGU guidelines were developed in this context, aiming to provide a structured framework for integrating pharmacogenetic testing into routine clinical care in Italy. They emphasize that i) pharmacogenetic testing should be performed in accredited laboratories using validated analytical approaches that ensure appropriate coverage of clinically relevant genes and variants, in accordance with international guidelines (standardization should therefore refer to quality requirements and interpretative frameworks, rather than to the use of specific analytical technologies); ii) pharmacogenetic analyses should be interpreted according to internationally recognized guidelines, including those from the Association for Molecular Pathology (AMP) [6], the Clinical Pharmacogenetics Implementation Consortium (CPIC) [7], and the Dutch Pharmacogenetics Working Group (DPWG) [8]. The SIGU Working Group recommends that testing should focus primarily on drug–gene pairs with the highest level of evidence (ClinPGx clinical annotation level 1 A), ensuring both clinical validity and therapeutic utility. This prioritization reflects the current scope of the SIGU recommendations and is intended to support a harmonized national implementation; it does not preclude the future inclusion of additional gene–drug pairs as evidence evolves and consensus strengthens.

A crucial aspect of the SIGU recommendations concerns the ethical and organizational principles underpinning test implementation. Patients must receive appropriate pre-test counselling and provide informed consent, particularly when pharmacogenetic information is derived as a secondary or incidental finding during NGS analyses performed for other diagnostic indications. The guidelines specify that only pharmacogenetic variants with proven clinical relevance and established actionability should be reported in this context. For example, only variants in RYR1 and CACNA1S with a confirmed association with malignant hyperthermia susceptibility should be reported as secondary findings, following ACMG and CPIC guidance and ClinGen interpretation, since they directly inform clinical management and anaesthetic safety.

The SIGU Working Group also defines the professional roles involved in pharmacogenetic testing. Data analysis and interpretation should be supervised by geneticists, while therapeutic implications must be discussed in collaboration with clinical pharmacologists or relevant specialists. The final report should clearly indicate the gene–drug pair investigated, the diplotype and predicted phenotype, and the corresponding therapeutic recommendations, following the logic of DPWG or AMP guidelines. Laboratories performing such analyses must operate under robust quality assurance frameworks compliant with international standards, including participation in external proficiency testing.

The economic dimension of pharmacogenetic testing is also addressed. Evidence from the pre-emptive 12-gene panel approach used in the PREPARE study demonstrates that genotype-guided prescribing can reduce clinically relevant adverse drug reactions by approximately 30% [9]. While the primary study focused on safety, a subsequent multinational cost-utility analysis confirmed that this strategy is cost-effective. In a pre-emptive scenario (e.g., a 'pharmacogenetic passport'), the approach becomes cost-saving, with estimated savings of €103.6 per patient due to reduced hospitalizations [10]. The SIGU guidelines therefore, advocate the integration of pharmacogenetic testing as a cost-effective tool to enhance therapeutic precision and sustainability within the SSN. The document further calls for national research efforts to evaluate the health-economic impact of pharmacogenetic implementation in the Italian context and to collect real-world data supporting broader adoption.

As pharmacogenetics becomes an integral part of personalized medicine, SIGU recognizes the need for continuous education among healthcare professionals. Training programs in medical genetics, pharmacology, and molecular diagnostics should include pharmacogenetic competencies, ensuring that clinicians and pharmacists can interpret and apply test results appropriately. Genetic counselling services are expected to play an increasingly important role in supporting patients to understand pharmacogenetic information -- ensuring that communication remains focused on individual clinical management while respecting medical confidentiality—and facilitating multidisciplinary communication across the healthcare continuum.

The SIGU Working Group on Pharmacogenomics was composed of experts from academia, clinical genetics services, and research institutions across Italy. Its members collaborated to review international standards, analyse European policy frameworks, and assess the ethical, technical, and economic implications of germline pharmacogenetic testing. The recommendations were refined through internal consultation and approved by the SIGU Executive Board after external expert review.

In conclusion, the SIGU recommendations provide a comprehensive roadmap for the responsible and standardized use of germline pharmacogenetic testing in Italy. They promote an evidence-based, ethically sound, and economically sustainable approach to the integration of pharmacogenetics into clinical care. By aligning with international best practices and emphasizing patient-centred implementation, these guidelines aim to enhance therapeutic safety, optimize drug efficacy, and advance the broader goals of precision medicine within the Italian healthcare system.

DETAILED LIST OF SIGU RECOMMENDATIONS FOR GERMLINE PHARMACOGENETIC TESTING

For the implementation of germline pharmacogenetic testing in routine clinical practice within the Italian National Health Service (SSN), SIGU considers that the following points must be carefully addressed:

1. **Prescription and informed consent**. The prescription of pharmacogenetic tests is the responsibility of the treating physician who manages the patient's drug therapy. However, to ensure clinical appropriateness, SIGU recommends a multidisciplinary approach. The Medical Geneticist and the Clinical Pharmacologist should support the prescribing physician in identifying the most appropriate markers and in interpreting complex results. This collaborative model ensures that PGx data are correctly integrated into the clinical decision-making process while maintaining clear accountability for the final therapeutic choice. Patients must receive comprehensive pre-test information and genetic counselling and must provide specific informed consent for pharmacogenetic testing. Testing and reporting should be limited to the scope of the consent provided, to avoid disclosure of information the patient did not agree to receive.
2. **Priority and workflow for variant selection and reporting**. Centres performing pharmacogenetic testing should primarily adhere to mandatory requirements and drug labels issued by regulatory agencies (e.g., EMA, AIFA). In the absence of specific regulatory mandates, variants should be selected and phenotypes defined in accordance with the following evidence-based hierarchy: (1) follow AMP recommendations (specifically ClinPGx 1 A evidence) where available; (2) if AMP is not available, use DPWG guidance; (3) if DPWG guidance is not available (for genes of primary interest, e.g., mt-RNR1), refer to CPIC. This tiered approach ensures harmonized decision-making in case of discrepancies between databases and should be applied both to the selection of variants to be tested and the reporting of diplotypes and phenotypes. The laboratory report should explicitly state the guideline used for clinical interpretation.
3. **Reporting of secondary pharmacogenetic findings**. When laboratories extract pharmacogenetic information from data generated for other diagnostic purposes, the same guideline hierarchy (AMP → DPWG → CPIC) and the same evidence threshold (ClinPGx clinical annotation level 1 A [11]) must be applied before reporting secondary findings. SIGU explicitly recommends that, among secondary findings, pathogenic or likely-pathogenic variants in *RYR1* and *CACNA1S* (malignant-hyperthermia susceptibility) should be reported, given their direct clinical relevance for anaesthetic management.
4. **Quality assurance and professional roles**. Testing must be performed in SSN-accredited laboratories operating under a robust quality-assurance framework (e.g., ISO standards, external proficiency testing). Data analysis and variant interpretation should be performed by a geneticist, while the resulting pharmacogenetic report should be transmitted to a clinical pharmacologist or relevant prescribing specialist for integration into therapeutic decision-making.
5. **Evidence of net benefit and health-system readiness**. Implementation should be supported by robust evidence demonstrating that the benefits of testing outweigh potential harms (e.g. reduction in adverse drug reactions versus risk of over-medicalization or misinterpretation). SIGU recommends pharmaco-economic and outcomes research, including prospective studies like PREPARE, to inform LEA inclusion and reimbursement policies. Moreover, the health-system capacity (laboratory throughput, clinical follow-up, specialist availability) must be assessed and strengthened before large-scale implementation.
6. **Ethics, data protection and consent architecture**. Pharmacogenetic testing must comply with (GDPR) and national laws on genetic data before large-scale implementation; informed-consent documents should explicitly consider the possibility of pharmacogenetic secondary findings and detail the procedures of data storage, sharing and re-interpretation over time.
7. **Research needs — psychosocial and organizational**. There is an urgent need for empirical research on the psychosocial impact of pharmacogenetic testing, including patients' understanding, perception and behavioural responses, and as well as on organizational models for integrating pharmacogenomics into clinical management and healthcare pathways. Such research should inform implementation strategies, educational initiatives, ad training programmes for healthcare professionals.
8. **Digital integration**. To ensure that pharmacogenetic testing translates into improved patient outcomes, results must be actionable at the point of care [11–14]:

    1) Clinical Decision Support: SIGU advocates for the integration of PGx data into Electronic Health Records (EHR) supported by Clinical Decision Support Systems

(CDSS). These systems should provide real-time alerts and prescribing recommendations based on established guidelines (e.g., DPWG, CPIC).
2) Primary Care & Pharmacy Involvement: The implementation model must extend beyond genomic hubs to include General Practitioners (GPs), who are essential for managing long-term therapies and preventing DDI (Drug-Drug-Gene Interactions) in the community setting.
3) Dynamic Records: PGx information should be treated as a lifelong clinical resource, updated as new evidence emerges, and maintained across different care settings.

REFERENCES

1. SIGU recommendations for performing germline pharmacogenetic testing, https://sigu.net/wp-content/uploads/2025/10/Raccomandazioni-SIGU-per-lesecuzione-di-test-farmacogenetici-germinali_finale-def.pdf.
2. Pirmohamed M. Pharmacogenomics: current status and future perspectives. Nat Rev Genet. 2023;24:350–62. https://doi.org/10.1038/s41576-022-00572-8.
3. Floris M, Moschella A, Alcalay M, Montella A, Tirelli M, Fontana L, et al. Pharmacogenetics in Italy: current landscape and future prospects. Hum Genomics. 2024;18:78. https://doi.org/10.1186/s40246-024-00612-w.
4. Osanlou R, Walker L, Hughes DA, Burnside G, Pirmohamed M. Adverse drug reactions, multimorbidity and polypharmacy: a prospective analysis of 1 month of medical admissions. BMJ Open. 2022;12:e055551 https://doi.org/10.1136/bmjopen-2021-055551.
5. SIF-AIOM & fluoropyrimidines, irinotecan. https://www.aiom.it/2024-aiom-sif-raccomandazioni-per-analisi-farmacogenetiche/.
6. Pratt VM, Cavallari LH, Fulmer ML, Gaedigk A, Hachad H, Ji Y, et al. DPYD Genotyping Recommendations: A Joint Consensus Recommendation of the Association for Molecular Pathology, American College of Medical Genetics and Genomics, Clinical Pharmacogenetics Implementation Consortium, College of American Pathologists, Dutch Pharmacogenetics Working Group of the Royal Dutch Pharmacists Association, European Society for Pharmacogenomics and Personalized Therapy, Pharmacogenomics Knowledgebase, and Pharmacogene Variation Consortium. J Mol Diagn. 2024;26:851–63. https://doi.org/10.1016/j.jmoldx.2024.05.015.
7. Relling MV, Klein TE. CPIC: Clinical Pharmacogenetics Implementation Consortium of the Pharmacogenomics Research Network. Clin Pharmacol Ther. 2011;89:464–7. https://doi.org/10.1038/clpt.2010.279.
8. Lunenburg CATC, van der Wouden CH, Nijenhuis M, Crommentuijn-van Rhenen MH, de Boer-Veger NJ, Buunk AM, et al. Dutch Pharmacogenetics Working Group (DPWG) guideline for the gene-drug interaction of DPYD and fluoropyrimidines. Eur J Hum Genet. 2020;28:508–17. https://doi.org/10.1038/s41431-019-0540-0.
9. Swen JJ, van der Wouden CH, Manson LE, Abdullah-Koolmees H, Blagec K, Blagus T, et al. A 12-gene pharmacogenetic panel to prevent adverse drug reactions: an open-label, multicentre, controlled, cluster-randomised crossover implementation study. Lancet. 2023;401:347–56. https://doi.org/10.1016/S0140-6736(22)01841-4.
10. Fragoulakis V, Swen JJ, Koufaki MI, Blagec K, Blagus T, Böhringer S, et al. Multinational cost-utility analysis of panel-based pharmacogenetics-guided treatment of patients enrolled in the U-PGx PREPARE study. EClinicalMedicine. 2025;91:103686. https://doi.org/10.1016/j.eclinm.2025.103686.
11. Whirl-Carrillo M, Huddart R, Gong L, Sangkuhl K, Thorn CF, Whaley R, et al. An Evidence-Based Framework for Evaluating Pharmacogenomics Knowledge for Personalized Medicine. Clin Pharmacol Ther. 2021;110:563–72. https://doi.org/10.1002/cpt.2350.
12. McDermott JH, Tsakiroglou M, Newman WG, Pirmohamed M. Pharmacogenomics in the UK National Health Service: Progress towards implementation. Br J Clin Pharmacol. 2025;91:2241–50. https://doi.org/10.1002/bcp.70109.
13. Sharma V, McDermott J, Keen J, Foster S, Whelan P, Newman W. Pharmacogenetics Clinical Decision Support Systems for Primary Care in England: Co-Design Study. J Med Internet Res. 2024;26:e49230 https://doi.org/10.2196/49230.
14. McDermott JH, Wright S, Sharma V, Newman WG, Payne K, Wilson P. Characterizing pharmacogenetic programs using the consolidated framework for implementation research: A structured scoping review. Front Med (Lausanne). 2022;9:945352. https://doi.org/10.3389/fmed.2022.945352.

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AUTHOR CONTRIBUTIONS

MF conceived the study and wrote the first draft of the manuscript. AM, MC, MA, MRI, PG, and MRM contributed to the writing and critically revised the manuscript. All authors read and approved the final version of the manuscript.

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COMPETING INTERESTS

The authors declare no conflict of interest.

ETHICAL APPROVAL

Ethical approval was not required for this study as it did not involve experiments on human subjects.

ADDITIONAL INFORMATION

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