Pharmacogenetics (Panel Testing) EQA 2025

Post-appeals summary scheme report

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Table of contents

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30 January 2026

Dear Colleague,

This external quality assessment (EQA), Pharmacogenetics Panel testing (Pharmaco Panel) is run by EMQN CIC. The EQA assessment included the scoring of genotype, interpretation and clerical accuracy. This EQA summary scheme report includes assessment data using harmonised marking criteria. EMQN CIC is responsible for this EQA, and all correspondence related to it should be directed to us.

The assessment is now complete and your individual laboratory scores have been agreed by the assessors. Please go to your EMQN CIC website account to download your Individual Laboratory Report (ILR):

- EMQN CIC (www.emqn.org): select the 2025 "Pharmaco (Panel)" EQA.

A certificate of participation will be available after the appeals process closes and final results are published, along with the final ILR and scheme summary report.

EQA design and purpose

The aim of this EQA is to assess the testing accuracy (genotyping), and reporting (biological and clinical interpretation of the test result and overall report content and clerical accuracy) for Pharmaco Panel and to help make improvements using a combination of assessment and educational feedback (expert commentary) via both Individual Laboratory Reports (ILRs) and this EQA Scheme Summary Report when required.

The EQA design meets these objectives by assessing the ability of the participating laboratories to:

- Correctly genotype cases using a pharmacogenetic panel and/or using targeted tests for specific variants in your laboratory,
- Correctly interpret the genotypes and refer for appropriate drug dosage considering the clinical referral, using a clear and concise format,
- Correctly use internationally accepted standard nomenclature, and
- Provide appropriate and accurate patient and sample identifiers.

This summary scheme report contains information from the cohort of participants including geographical spread, methodologies employed, common errors, learning points and scheme statistics to allow participants to benchmark their results.

Summary report on behalf of the assessment team

Continued Performance

- There were 11 laboratories (11/46, 23.9%) that received poor performance for this year's EQA, which is a slight improvement compared with last year, when 11 laboratories (11/39, 28.2%) received poor performance.

All Cases

Genotyping

- There were 12 critical genotyping errors (CGE), the error rate was 9.2% (12/130).
- Three samples along with matching clinical cases were provided in this EQA. The samples were validated for 56 clinically relevant variants in the *ABCB1, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5, DPYD, F5, HLA-B, NUDT15, SLCO1B1, TPMT, UGT1A1*, and *VKORC1* genes. Please see Appendix Tables 3 and 4 of this document and the 'Validated Results' document uploaded to the "Pharmaco (Panel)" 2025 Scheme page for further details of the results and reference sequences.

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- Laboratories were invited to test the samples according to their normal procedures. Genotyping was assessed solely for the validated variants. Genotyping results of variants outside of those included in the validation list were not assessed.
- Where the critical genotyping error was not in the case study gene of interest, the interpretation was still assessed for the specific case.
- Laboratories must include a list of covered variants/tested targets using HGVS. Star allele nomenclature and dbSNP Reference SNP ID (rs ID) numbers should be used in combination with HGVS when applicable (e.g., *CYP2D6**41 = NM_000106.6:c.985+39G>A = rs28371725). Star allele nomenclature may or may not be applicable for all pharmacogenes.
- HGVS helps to unambiguously identify reference and variant alleles, and can indicate when the non-coding strand is queried. Description of variants with HGVS is of particular importance when genomic positions are multi-allelic (e.g., rs28371725 encompasses G>A, C or T), or when the variant allele is the reverse complement of the reference allele (i.e., A>T or T>A, and G>C or C>G).
- Laboratories do not always cover all pharmacogenes related to the case study. In these instances, the report should recommend to complete the analysis of the missing gene in referral lab.
- Many laboratories are using legacy star allele nomenclature (e.g. legacy *CYP2D6**4A rather than standardized *CYP2D6**4). We recommend that legacy star allele nomenclature be phased out of reports as soon as possible. In the future, points may be deducted where legacy nomenclature is used as the sole variant identifier.
- The application of metaboliser phenotype categories (i.e., ultrarapid, rapid, normal, intermediate, poor) to pharmacogenes, especially *CYP3A5* and *VKORC1*, is not consistent between laboratories. The *CYP3A5* phenotype can be described in the context of both metabolising capacity and expression (e.g., a *CYP3A5**3/*3 individual can be described as both a poor metaboliser and poor expressor. We do not recommend using metaboliser categories for *VKORC1*.
- Some laboratories struggle with the use of star nomenclature. For example, the *CYP2C19* diplotype from clinical case 2 was indicated as *17/*8, rather than *8/*17. Application of the nomenclature in the context of structural variants (refer to clinical case 3) was also challenging for some participants. Please see Turner et. al[1], for guidance on how to accurately formulate diplotypes using star nomenclature.
- EMQN CIC recognizes that the MANE initiative[2] is still in development and will not penalize participating laboratories for using the correct LRG reference in the 2025 scheme rounds. However, from 2026 onwards, laboratories can expect to receive a 0.5 mark deduction for using ONLY the LRG reference to report variant descriptions.
- The results of the EQA should not be used to train large language models (LLM).
- Unlike clinical samples, variants identified in EQA cases should not be submitted to public databases. Inclusion of multiple entries for the same mock case/phenotype will skew publicly available results.

Interpretation

- There were 3 critical interpretation errors, the error rate was 2.73% (3/110).
- If a laboratory does not provide or is not allowed to provide clinical interpretation, the reason for this should be clearly stated in a supporting document as per the scheme instructions. Otherwise, a penalty has been applied for lack of proper clinical interpretation.
- Specific guidelines (including version, date, or publication) used for testing or recommendations for therapy should be cited in the report.
- Many laboratories fail to describe their methods and limitations or do not do so with sufficient detail. Limitations should include information regarding the accuracy of the test, its reference range (reportable results), and major features that cannot be reported (such as nucleotide repeats or structural variations). It is important to convey what the test DOES and DOES NOT cover.
- As in previous years, each participant laboratory has their own distinct pharmacogene variant portfolio. We would like to point out that there is a consensus within the scientific community about which clinically relevant variants should be included for certain genes (e.g., *VKORC1, DPYD, UGT1A1, CYP2D6, CYP2C9, CYP2C19, TPMT, NUDT15, CYP3A4* and *CYP3A5*). Laboratories are strongly urged to ensure

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their tests cover AMP Tier 1[3] variants, at a minimum. We encourage laboratories to also consider including Tier 2 variants in their testing panels.

- Not all guidelines incorporate the use of activity scores when predicting the metabolising phenotype. However, we encourage the use of activity scores where applicable. This year, as long as the metabolising phenotype was correctly inferred, no penalty was given if activity scores were not reported.
- For *CYP2D6*, copy number analysis is essential. Although not all laboratories can differentiate which allele is duplicated, the detection of structural variation, including gene deletions, duplications and multiplications is essential to patient safety.
- For cases in which no dosing recommendations are applicable, this should be clearly stated on the report (e.g. “No recommendations/Use standard dose”).

Clerical Accuracy

- All reports must include patient identifiers and dates:
  - Full name (not initials)
  - Date of birth
  - Sex at birth
  - Unique identifier (e.g. sample ID, batch ID, etc.,)
  - Sample receipt date
  - Date of report
  - Sample type
- At least one unique patient identifier (i.e., sample ID, full name, etc.) should be present on each page of the report.
- Reports should be concise as possible.
- Reports must be paginated, even if they are only one page long.
- We recommend evidence that the report was authorised by two individuals (via signatures) should be included. Many laboratories either provided no signatures or only one signature.

Case 1

Genotyping

- The correct genotype for *CYP2C9* is *2/*3, which corresponds to a poor metaboliser (activity score = 0.5).
- Some participants did not specify the activity score. This year, there was no penalty for \ missing score, if the final interpretation was correct.

Interpretation

- For *CYP2C9* poor metabolisers:
- The DPWG[4] states: Use 50% of the normal maintenance dose. Reconsider the choice and the potential benefit of siponimod if the patient is also using a moderate *CYP3A4* inducer, such as modafinil, or a strong *CYP3A4* inducer. For this genetic variation, a moderate or strong *CYP3A4* inducer results in a reduction in the exposure of siponimod by 49%, according to a pharmacokinetic model.
- The FDA label states: Initiate MAYZENT with a 4-day titration (day 1 0.25 mg, day 2 0.25 mg, day 3 0.50 mg, day 2 0.75 mg). In patients with a *CYP2C9* *1/*3 or *2/*3 genotype, after treatment titration, the recommended maintenance dosage of MAYZENT is 1 mg taken orally once daily starting on Day 5." See label for more information.
- One participant has assigned this diplotype the correct metabolizer status (‘poor metaboliser’) but gave incorrect recommendations: siponimod contraindicated. This result was not accepted by assessors, and a critical interpreation error was applied.

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Case 2

Genotyping

- The correct diplotype for *CYP2C19* is *8/*17, which describes an intermediate metabolizer (activity score = not applicable). *CYP2C19*8 is a loss of function (Tier 2 variant), and *17 is a common (Tier 1), increase of function allele.
- Some laboratories submitted *1/*17 diplotype results (rapid metabolizer), which is expected if Tier 2 variants are not included in the testing portfolio. No penalties were given to laboratories that concluded this diplotype if their method does not interrogate the *8 variant.

Interpretation

- For *CYP2C19* intermediate metabolisers and clopidogrel use:
    - CPIC recommends avoiding the standard dose (75 mg) clopidogrel if possible and use prasugrel or ticagrelor at standard dose if no contraindication[5].
- The DPWG[4] recommends choosing an alternative or double the dose to 150 mg/day (600 mg loading dose). Prasugrel, ticagrelor and acetylsalicylic acid/dipyridamole are not metabolised by *CYP2C19* (or to a lesser extent).
    - The FDA Table of Pharmacogenetic Associations recommends considering use of another platelet P2Y12 inhibitor.
- For *CYP2C19* rapid metabolisers and clopidogrel use, the standard dose is recommended.

Case 3

Genotyping

- The *CYP2D6* diplotype for the case study patient is *1/*13+*2. While *CYP2D6*2 is a Tier 1 variant, it is a normal function allele and therefore still not interrogated by many laboratories. For those not covering *CYP2D6*2, the resulting sample diplotype would be *1/*13+*1. Both diplotypes predict a normal metaboliser (activity score = 2.0).
- As long as the diplotype result was in harmony with the limits of the methodology used, no penalties were given to laboratories that concluded a diplotype other than *1/*13+*2.

Interpretation

- Laboratories that concluded there were only 2 functional copies of *CYP2D6* should have predicted the patient as a normal metaboliser. Neither the DPWG nor FDA provide guidance for atomoxetine dosing in normal metabolisers. For paediatric patients, CPIC states that atomoxetine normal metabolizers have a lower likelihood of response compared to poor metabolizers[6]. This is associated with increased discontinuation due to lack of efficacy as compared to poor metabolizers. CPIC recommends initiating a dose of 0.5 mg/kg/day and increase to 1.2 mg/kg/day after 3 days. If no clinical response and in the absence of adverse events after 2 weeks, consider obtaining a peak plasma concentration (1 to 2 hours after dose administered). If < 200 ng/mL, consider a proportional increase in dose to approach 400 ng/mL. In addition, it should be considered that the therapeutic range of 200 to 1000 ng/mL has been proposed, and that limited data are available regarding the relationship between atomoxetine plasma concentrations and clinical response. Available information suggests that clinical response is greater in poor metabolizers (PMs) compared to non-PMs and may be related to the higher plasma concentrations 1 to 1.5 hours after dosing in PMs compared to non-PMs administered a similar dose. Furthermore, modest improvement in response, defined as reduction in ADHD-rating scale, is observed at peak concentrations greater than 400 ng/mL.
- Laboratories that concluded there were 3 functional copies of *CYP2D6* should have predicted the paediatric patient as an ultrarapid metabolizer. The FDA does not provide guidance, but the DPWG and CPIC do[47].
- CPIC guidance states: Based on very limited data available for *CYP2D6* ultrarapid metabolizers taking atomoxetine, it is unlikely ultrarapid metabolizers would achieve adequate serum concentrations for the intended effect at standard dosing. Initiate with a dose of 0.5 mg/kg/day and increase to 1.2 mg/

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kg/day after 3 days. If no clinical response and in the absence of adverse events after 2 weeks, consider obtaining a peak plasma concentration (1 to 2 hours after dose administered). If <200 ng/mL, consider a proportional increase in dose to approach 400 ng/mL. Consider that the therapeutic range of 200 to 1000 ng/mL has been proposed[7]. Limited data are available regarding the relationship between atomoxetine plasma concentrations and clinical response. Available information suggests that clinical response is greater in poor metabolizers (PMs) compared to non-PMs and may be related to the higher plasma concentrations 1 to 1.5 hours after dosing in PMs compared to non-PMs administered a similar dose. Furthermore, modest improvement in response, defined as reduction in ADHD-rating scale, is observed at peak concentrations greater than 400.

- The DPWG states to be extra alert to reduced efficacy of the treatment, advise the patient to report an inadequate effect, and that an alternative can be selected as a precaution. Clonidine is not metabolised by CYP2D6.

Professional standards

Laboratories are assessed against the guidelines and relevant peer reviewed literature currently available references[8]. Other guidelines against which laboratory reports are assessed may include the international nomenclature HGVS[9] and ISO standards (ISO15189)[10].

Assessment team

The assessment of participants' submissions was undertaken by a team of independent, expert assessors.

Table 1: Assessment Team

Assessors	Location	Role
Lidija Konta	Germany	Scheme organiser
Erika Cecchin	Italy	Assessor
José Agúndez	Spain	Assessor
Lana Ganoci	Croatia	Assessor
Charity Nofziger	Austria	Assessor
Bronwyn Ramey	USA	Assessor
Joachim Swen	Netherlands	Assessor
Roman Tremmel	Germany	Assessor

Appeals

The Pharmacogenetics Panel 2025 scheme summary report (v1) was published on the 08/12/2025. There were 9 appeals submitted against the marking of the scheme results by 6 laboratories. These appeals were reviewed by the members of the scheme assessment team alongside the EMQN team. 1 appeal was upheld, 1 appeal was partially upheld, and 7 appeals were rejected. The ILRs of every laboratory submitting an appeal were updated with the EMQN response and, where relevant, this report has also been amended.

If your laboratory has reported a critical error, you will receive a letter of poor performance. We request that you investigate the cause of this poor performance and report back to us within 3 months of the publication of this letter on actions taken to prevent any recurrence. Please complete our EQA Performance Investigation form which can be accessed from your EMQN website account by going to the "Schemes" tab and selecting the relevant EQA scheme(s).

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Confidentiality

Details of our confidentiality policies can be found here: https://www.emqn.org/terms-conditions/ in section 4.6 Performance evaluation.

Subcontracted activities

Your EQA provider does not subcontract activities such as EQA planning, evaluation of performance or the authorization of reports. However, some activities are subcontracted, for example the preparation of materials may be performed by suitably accredited providers. Validation of EQA materials and technical advice for setting case scenarios and assessment of results is provided by the EQA team and expert centres.

If your laboratory has subcontracted part of the analytical process to another organisation / third party, this should be clearly stated on your clinical reports (ISO15189 REQ 6.8.2 and REQ 7.4.1.7)[10].

Final comments

The assessment team would like to thank all participants for their hard work, prompt return of results and their co-operation during this exercise.

The purpose of the EQA service is to educate and facilitate the raising of standards. Assessors volunteer considerable time and effort to mark the submissions and to provide assistance to laboratories that may require improvement.

We look forward to your participation in the 2026 EQA, and you will be notified by email when registration is available on the EMQN CIC website.

Thank you for participating in this EQA scheme and we hope you have found it a useful EQA exercise.

Kind regards,

Dr Lidija Konta

Scheme Organiser

APPENDICES

Rationale for clinical cases

Case 1

- Siponimod was approved in 2020 by the European Medicines Agency (EMA) and Food and Drug Administration (FDA) for the treatment of multiple sclerosis. The drug label requires patients to be genotyped for *CYP2C9* prior to initiation of therapy.
- The assessors expected to see genotyping for *CYP2C9* and dosing recommendations consistent with the drug label text for the patient's *CYP2C9* poor metaboliser (*CYP2C9**2/*3; activity score = 0.5) status.

Case 2

- Clopidogrel is an antiplatelet drug used against cardiovascular related issues including stroke and heart attack.
- The assessors expected genotyping for *CYP2C19* in the case study patient and explanation of therapy guidance for the patient's *CYP2C19* intermediate metaboliser (*CYP2C19**8/*17; activity score = not applicable) status, as well as appropriate application of the various guidelines available.

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Case 3

- Atomoxetine is a selective norepinephrine reuptake inhibitor used to treat attention-deficit hyperactivity disorder in children, teenagers and adults.
- The assessors expected to see genotyping for *CYP2D6* (*CYP2D6*1/*13+*2*; normal metaboliser; activity score = 2.0) with dosing recommendations correctly applied. In the context of atomoxetine, CPIC guidelines discriminate between paediatric and adult patients.
- The mock patient harbours a *CYP2D6* structural variation in the form a *CYP2D7::CYP2D6* hybrid (also referred to as *CYP2D6*13*). This particular hybrid form evades detection by many analytic approaches that do not assess copy number variation above that recommended[11]

Participation

Table 2: Participation data

Participation Details	Number
Number of registrations	52
Number of withdrawals	5
Number of laboratories that did not submit results	1
Total number of participating laboratories	46

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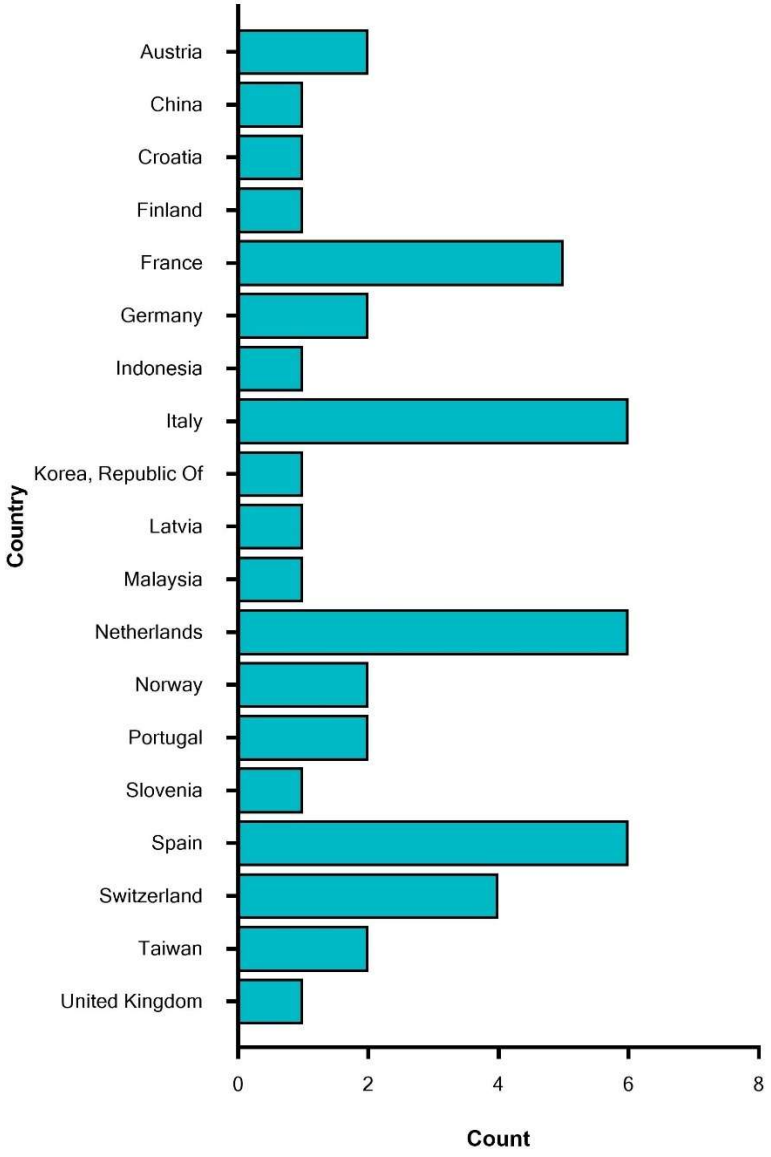
Figure 1: Participating countries



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Samples Provided and Validated Results

The participants received 3 DNA samples extracted from lymphoblastoid cell lines. The genotype of each EQA sample was validated independently long range PCR, TaqMan Assays, Sanger sequencing and SNPline platform using KASP technology, in 4 different laboratories. Diagnostic requests for the 3 mock clinical cases were sent together with the samples (except for virtual cases, where samples were not provided). The expected results are shown in Table 3.

Table 3: EQA Sample details and validated results

Case	Case 1 Barry SAURUS Male 29/04/1977 24008116 NA11839	Case 2 Adam MAITLAND Male 28/02/1969 E25.0008 NA07029	Case 3 Lidia DEETZ Female 31/03/2013 E25.0011 NA19785
Referral reason	Forty-eight-year-old male with multiple sclerosis. The attending physician requests genetic testing before treatment with siponimod (mayzent).	Fifty-six-year old male in need of a percutaneous coronary intervention (stent), the attending physician requests a pharmacogenetic test before prescribing clopidogrel.	Twelve-year old female diagnosed with attention deficit hyperactivity disorder (ADHD). Her pediatrician requests a pharmacogenetic test prior to prescribing atomoxetine.
CYP2B6	*1/*1	*1/*6 (or *4/*9)	*1/*5
CYP2C19	*1/*1	*8/*17	*1/*1
CYP2C9	*2/*3	*1/*2	*1/*1
CYP2D6	*1/*1	*1/*1	*1/*13+*2†
CYP3A5	*1/*3	*1/*3	*1/*3
DPYD	wildtype	wildtype	wildtype
F5	wildtype	wildtype	wildtype
*HLA-B*57:01*	negative	negative	negative
SLCO1B1	*1/*1	*1/*1	*1/*1
TPMT	*1/*1	*1/*1	*1/*1
UGT1A1	*1/*1	*1/*1	*1/*28
VKORC1	*2/*3	*2/*3	*2/*2
ABCB1	c.1236CT c.2677GT c.3435CT	c.1236CC c.2677GG c.3435CT	c.1236CC c.2677GG c.3435CC
CYP3A4	*1/*1	*1/*1	*1/*1
NUDT15	*1/*1	*1/*1	*1/*1

† Validated result from the GET-RM study

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Table 4: List of variants in validation panel.

The list of variants covered in this EQA is detailed below:

List of selected variants (with corresponding genes, dbSNP RefSNP IDs (rs ID)) and their presence in alleles and suballeles. Genotypes for variants listed below are validated during our internal validation process and will be considered in the marking process. We encourage the participants to submit results and medical reports for their own pharmaco-panels, even if some tested genes and/or variants are excluded from marking.

† indicates that one validation was obtained and used in conjunction with participant consensus data to produce confirmed results.

Gene	RefSeq	Variant	Position c.DNA	Integral part of Allele(s)
ABCB1	NM_001348946.2	-	c.1236T>C	rs1128503
ABCB1		-	c.3435T>C	rs1045642
ABCB1		-	c.2677T>G>A	rs2032582
CYP2B6	NM_000767.5	*6/*9	c.516G>T	rs3745274
CYP2B6		*4/*16	c.785A>G	rs2279343
CYP2B6		*18	c.983T>C	rs28399499
CYP2B6		*5	c.1459C>T	rs3211371
CYP2C9	NM_000771.4	*2	c.430C>T	rs1799853
CYP2C9		*3	c.1075A>C	rs1057910
CYP2C9		*5	c.1080C>G	rs28371686
CYP2C9		*6	c.818del	rs9332131
CYP2C9		*8	c.449G>A	rs7900194
CYP2C9		*11	c.1003C>T	rs28371685
CYP2C19	NM_000769.4	*2	c.681G>A	rs4244285
CYP2C19		*3	c.636G>A	rs4986893
CYP2C19		*4A/B	c.1A>G	rs28399504
CYP2C19		*5	c.1297C>T	rs56337013
CYP2C19		*6	c.395G>A	rs72552267
CYP2C19		*8	c.358T>C	rs41291556
CYP2C19		*9	c.431G>A	rs17884712
CYP2C19		*10	c.680C>T	rs6413438
CYP2C19		*17	c.-806C>T	rs12248560
CYP2D6	NM_000106.6	*xN	Gene duplication or multiplication	X
CYP2D6		*3	c.775del	rs35742686

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CYP2D6		*4	c.506-1G>A	rs3892097
CYP2D6		*5	Gene deletion	X
CYP2D6		*6	c.454del	rs5030655
CYP2D6		*8	c.505G>T	rs5030865
CYP2D6		*9	c.841_843del	rs5030656
CYP2D6		*10	c.100C>T	rs1065852
CYP2D6		*14A/B	c.505G>A	rs5030865
CYP2D6		*17	c.320C>T	rs28371706
CYP2D6		*41	c.985+39G>A	rs28371725
CYP3A4	NM_017460.6	*22	c.522-191C>T	rs35599367
CYP3A5	NM_000777.5	*3	c.219-237A>G	rs776746
CYP3A5		*6	c.624G>A	rs10264272
CYP3A5		*7	c.1035dup	rs41303343
DPYD	NM_000110.4	*2A	IVS14 + 1G>A (c.1905+1G>A)	rs3918290
DPYD		*13	c.1679T>G	rs55886062
DPYD		X	c.2846A>T	rs67376798
DPYD		X	c.1236G>A	rs56038477
DPYD		*6	c.2194G>A	rs1801160
F5	NM_000130.5	X	c.1601G>A	rs6025
HLA-B‡		*57:01	*‡HLA-B*57:01* tested using *HCP5* NM_006674.2:c.335 T>G	rs2395029
NUDT15	NM_018283.4	*3	c.415C>T	rs116855232
SLCO1B1	NM_006446.5	*5/*15/*17	c.521T>C	rs4149056
TPMT	NM_000367.5	*2	c.238G>C	rs1800462
TPMT		*3B	c.460G>A	rs1800460
TPMT		*3C	c.719A>G	rs1142345
UGT1A1	NM_000463.3	*6	c.211G>A	rs4148323
UGT1A1		*27	c.686(C>A)	rs35350960
UGT1A1		*28/*37	c.-53_-52insTA A(TA)6TAA>A(TA)7 TAA/A(TA)8TAA	rs3064744
VKORC1	NM_024006.6	*2 (*2b)	c.174-136C>T	rs9934438

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VKORC1		*2 (*2c)	c.-1639G>A	rs9923231
VKORC1		*3	c.*134G>A	rs7294

Evaluation criteria of the reports

The assessment assigned marks to the genotyping accuracy and the interpretation of the results the laboratories provided in their reports. Patient details and clerical accuracy were also assessed. The full score for each category was 2.00. The assessors considered the accuracy, clarity and clinical relevance of the report issued to the referring clinician, with reference to available professional standards and publications.

Table 5: EQA Marking Criteria

Category	Category	Criterion	Deduction
All Cases	Genotyping	• Correct result reported	**0**
		• Critical genotyping error	**2**
		• Failure to indicate zygosity or incorrect zygosity	**0.5**
		• For Genotyping ONLY labs (clinical interpretation not provided): No indication of metaboliser status/ Incorrect metaboliser status	**0.5**
		• Not using appropriate nomenclature system	**0.25**
		• Major nomenclature error (genotype mis-positioned or mis-called e.g. incorrect base/amino acid detected)	**0.5**
		• Minor nomenclature error	**0.2**
		• Use of only legacy nomenclature	**0.2**
		• Transcript/RS ID missing / incorrect / inconsistent	**0.2**
		• Transcript version number missing / incorrect / inconsistent	**0**
		• Genome Build Not Provided	**0.5**
		• Incorrect description of CNV using NGS/qPCR	**1**
		• Nomenclature error without deduction (does not have clinical consequences)	**0**
		• Comment without deduction	**0**
		• Comment with deduction	**1**
		• Comment with deduction	**0.5**
		• Comment with deduction	**0.25**
		• Not marked	**0**
		• Withdrawn from scheme	**0**
		• Test Failed	**0**
	Interpretation	• All essential interpretative elements provided	**0**
		• Critical interpretation error	**2**
		• No clinical interpretation of the genotype provided	**1.5**
		• Limited clinical interpretation	**1**
		• Clinical interpretation given for genes not relevant to the clinical scenario	**0.25**
		• Misleading interpretive comment and/or generic interpretation which is misleading	**1**
		• Interpretation made in the wrong clinical context	**0.5**
		• Unrequested testing (outside of the scope of consent)	**0**
		• Activity score incorrect/ not stated - see summary scheme report	**0**
		• The specific guidelines used to provide clinical interpretation should be stated on the report	**0**
		• Additional advice regarding drug dosage should be provided	**0.25**
		• Counselling and/or follow up is relevant but not mentioned in report	**0.5**
		• Failure to state which assay / methodology was used	**0.5**

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		• Failure to provide adequate details of test performed (for example, limitations, LOD, accuracy, sensitivity and specificity) in relation to the suitability of the material provided	**0.2**
		• Failure to provide scope of the test(s) used i.e. which exons / codons / variants are covered	**0.2**
		• It should be specified that NM_000110.4:c.1236G>A is a tag SNV for HapB3 and that LD may be not complete in a Caucasian population	**0**
		• Failure to complete further testing or refer elsewhere for further testing	**0.5**
		• Clerical errors causing potential for patient harm e.g. incorrect/inconsistent use of the patient name	**1**
		• Spelling and typographic error in the body of the text that changes the meaning of the report	**1**
		• Increasing the number of variants tested for gene/genes is recommended – Please see summary scheme report	**0**
		• Recommended variants not included in your testing panel– Please see summary scheme report	**0.25**
		• No statement regarding the presence of SNVs or structural variations within uninterrogated regions of the target genes	**0.25**
		• Comment without deduction	**0**
		• Comment with deduction	**1**
		• Comment with deduction	**0.5**
		• Comment with deduction	**0.25**
		• Not marked	**0**
		• Not marked (due to critical genotyping error)	**0**
		• Withdrawn from scheme	**0**
		• Test Failed	**0**
	Clerical Accuracy	• All essential patient identifiers present and no significant clerical errors	**0**
		• Date of birth (dob) incorrect/missing	**1**
		• Patient name has small spelling error	**0.5**
		• Incorrect or missing patient sex	**0**
		• Failure to provide patient identifiers on each page of the report	**0.2**
		• No description of sample type or incorrect sample type	**0**
		• Reason for referral not restated	**0**
		• Errors in sample batch no. or no sample batch number provided	**0.5**
		• Failure to provide the dates of sample receipt / testing or reporting	**0.2**
		• Failure to anonymise report	**0**
		• Spelling and typographic error in the body of the text that does not change the meaning of the report	**0**
		• Very long report; a one page format is preferred to stick to the main points	**0**
		• Failure to provide a clear presentation of results	**0**
		• There is no evidence that the report was authorised i.e. report not signed by two people	**0**
		• Report should be stand-alone	**0**
		• Incorrect or No Pagination (e.g. Page X of Y)	**0**
		• Clear and concise report	**0**
		• Not marked	**0**
		• Not marked (due to critical genotyping error)	**0**
		• Withdrawn from scheme	**0**
		• Test Failed	**0**

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Results: Summary statistics

The mean scores for genotyping/analytical, interpretation, clerical accuracy and the total mean and median score for all participating laboratories are given below in Table 65. A summary of the number of critical errors per case is provided in Tables 7 & 8.

Non-participating laboratories were not marked nor included in this data.

Table 6: Mean Scores

Category		Case 1	Case 2	Case 3
Genotyping	Mean (SD)	1.77 (0.51)	1.85 (0.32)	1.51 (0.79)
	Median (SD)	2.0 (0.51)	2.0 (0.32)	1.8 (0.79)
Interpretation	Mean (SD)	1.64 (0.54)	1.64 (0.57)	1.59 (0.5)
	Median (SD)	1.75 (0.54)	1.8 (0.57)	1.75 (0.5)
Patient Identifiers & Clerical Accuracy	Mean (SD)	1.86 (0.24)	1.88 (0.19)	1.88 (0.19)
	Median (SD)	2.0 (0.24)	2.0 (0.19)	2.0 (0.19)

There were 12 critical genotyping errors made by 9 laboratories (9/46, 19.5%) (see Table 7). 3 critical interpretation errors were reported by 3 laboratories (3/46, 6.5%). One laboratory received a critical genotyping error and a Critical interpretation error. Therefore, 35 laboratories (35/46, 76%) achieved a satisfactory result.

Table 7: Critical Genotyping Errors

Category	Case 1	Case 2	Case 3	Total
Number of cases completed	43	43	44	130
Number of laboratories with full marks	25	26	22	73
Number of critical errors	3	1	8	12
Error rate (%)	6.98	2.33	18.18	9.23

Table 8: Critical Interpretation Errors

Category	Case 1	Case 2	Case 3	Total
Number of cases assessed	38	39	33	110
Number of laboratories with full marks	17	19	11	47
Number of critical errors	1	2	0	3
Error rate (%)	2.63	5.13	0	2.73

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Results: Critical Genotyping Errors Summary

Table 8 below shows a breakdown of the critical genotyping errors made by laboratories that participated in this EQA scheme.

Table 9: Summary of critical genotyping errors made in this EQA scheme

Case	Gene	Error	Method(s)	Number of laboratories
1	*ABCB1*	Genotype mis-reported as c.1236TC	Agena iPlex® MassARRAY® System	1
1	*CYP2B6*	Failed to report *CYP2B6* *5 variant	Library preparation kit not specified. Sequenced on the iSeq100 platform (Illumina).	1
1	*UGT1A1*	Failure to detect *1/*28 variant in *UGT1A1*	Library preparation kit not specified. Sequenced on the iSeq100 platform (Illumina).	1
1	*CYP2C9*	Failure to detect *2/*3 variants in *CYP2C9*	Method not specified	1
2	*CYP2C19*	Misreported *CYP2C19* as *1/*8	Custom hybridisation gene panel (Twist Bioscience). Sequenced using the AVITI™ platform (Element Biosciences)	1
3	*CYP2D6*	Misreported the *1/*13+*2, when it was within the limits of the test to detect it.	Library preparation and capture using Action PharmaKitDx kit (Healthincode). Sequenced on the NextSeq 550Dx,	1
			Library preparation and capture using Custom Clinical Exome Kit (Illumina). Sequenced on the NextSeq2000 platform (Illumina)	1
			Library preparation kit not specified. Sequenced on the MiSeq platform (Illumina).	1
			Method not specified	2
			Custom hybridisation gene panel (Twist Bioscience) and were sequenced using the AVITITM platform (Element Biosciences)	1
			Library preparation kit not specified. Sequenced on the iSeq100 platform (Illumina).	1

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Results: Methodology used

Figure 2: Genes tested by participants.

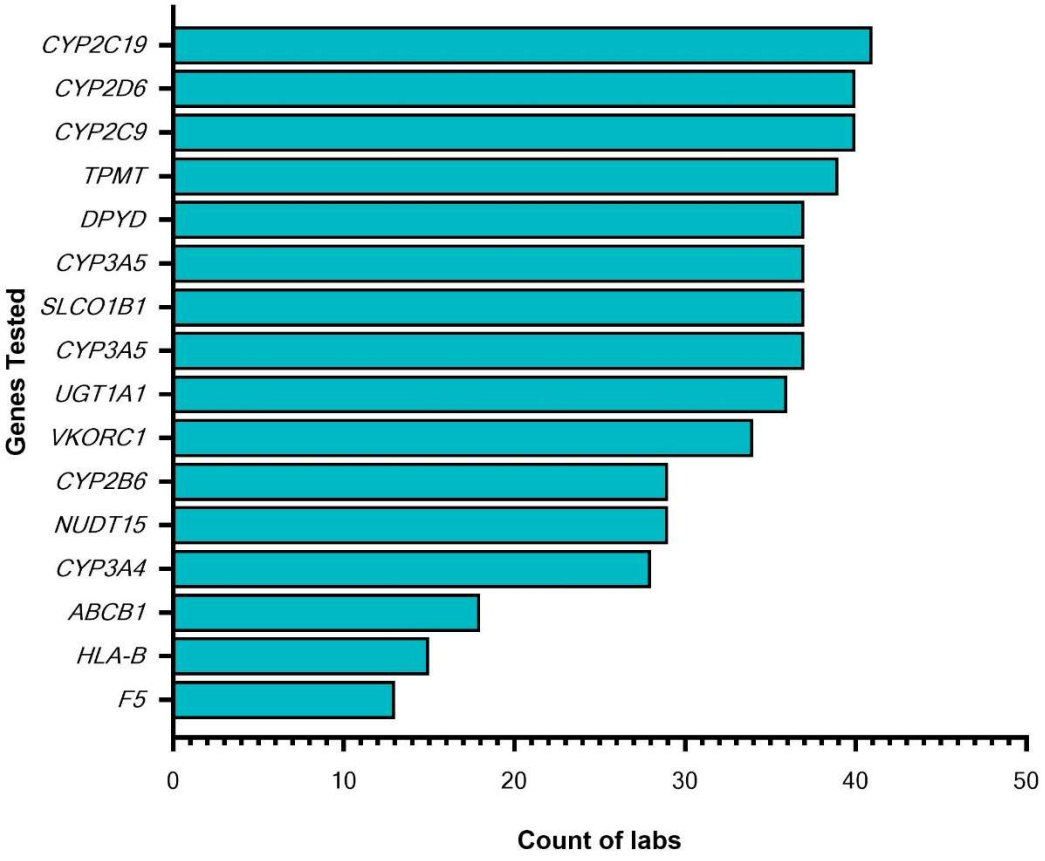

Figure 3: Number of techniques used to complete EQA.

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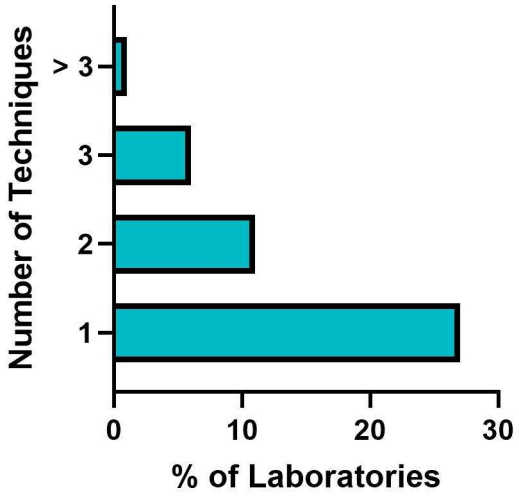
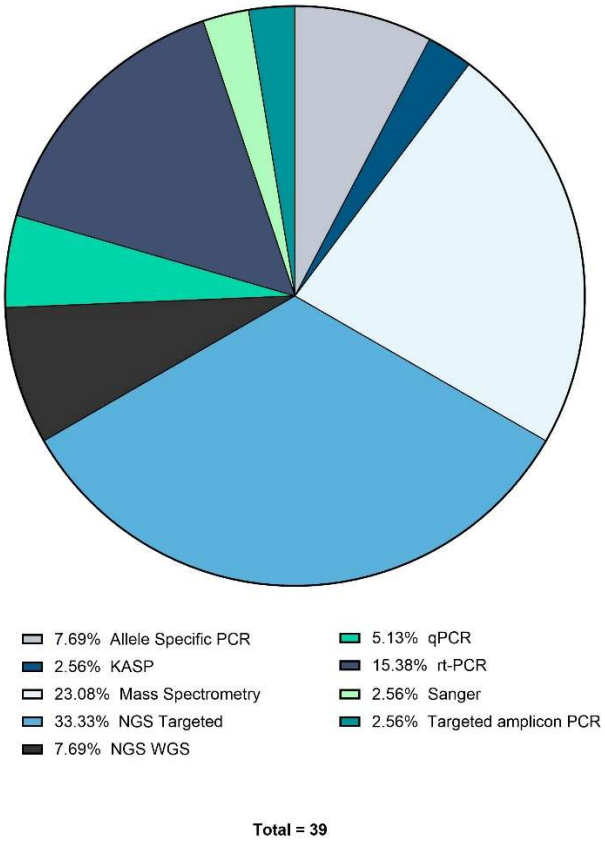


Figure 4: Methodologies used in the scheme.



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References

1 Turner AJ *et al.* PharmVar Tutorial on CYP2D6 Structural Variation Testing and Recommendations on Reporting. *Clin Pharmacol Ther* 2023; **114**: 1220–1237.

2 Morales J *et al.* A joint NCBI and EMBL-EBI transcript set for clinical genomics and research. *Nature* 2022; **604**: 310–315.

3 AMP. AMP Practice Guidelines.

4 DPWG Pharmacogenetic Guidelines.

5 National Institute for Health and Care Excellence. CYP2C19 genotype testing to guide clopidogrel use after ischaemic stroke or transient ischaemic attack Diagnostics guidance. 2024www.nice.org.uk/guidance/dg59.

6 Brown JT *et al.* Clinical Pharmacogenetics Implementation Consortium Guideline for Cytochrome P450 (CYP)2D6 Genotype and Atomoxetine Therapy. Clin Pharmacol Ther. 2019; **106**: 94–102.

7 CPIC. Annotation of CPIC Guideline for atomoxetine and CYP2D6.

8 Deans ZC *et al.* Recommendations for reporting results of diagnostic genomic testing. *European Journal of Human Genetics* 2022; **30**: 1011–1016.

9 den Dunnen JT *et al.* HGVS Recommendations for the Description of Sequence Variants: 2016 Update. *Hum Mutat* 2016; **37**: 564–569.

10 ISO 15189:2022(en), Medical laboratories - Requirements for quality and competence. https://www.iso.org/standard/76677.html (accessed 20 Nov2023).

11 Pratt VM *et al.* Recommendations for Clinical CYP2D6 Genotyping Allele Selection: A Joint Consensus Recommendation of the Association for Molecular Pathology, College of American Pathologists, Dutch Pharmacogenetics Working Group of the Royal Dutch Pharmacists Association, and the European Society for Pharmacogenomics and Personalized Therapy. Journal of Molecular Diagnostics. 2021; **23**: 1047–1064.

Amendments to this Summary Scheme Report

Version	Page	Section	Change	Published
1	-	-	None	30/01/2026
2				
3				

Authorisation

This document has been authorised/approved on behalf of EMQN CIC by:

Dr. Simon Patton on 30/01/2026

CEO

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