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Pharmacogenomics has two evidence bases, not one: Specific gene-drug pairs against panel-based pre-emptive testing for preventing adverse drug reactions

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Abstract

Background: Pharmacogenomic testing is advocated to prevent adverse drug reactions, and a large cluster-randomised trial of a 12-gene panel reporting a 30% reduction is widely cited as establishing the strategy. Specific gene-drug pairs have separately been shown to produce much larger effects. These two bodies of evidence are routinely presented as one. **Objectives:** To compare the magnitude of effect achieved by pre-emptive panel testing against that achieved by intervention on individual gene-drug pairs; to express both as numbers needed to treat and to screen; and to examine whether the genotype or the accompanying dose action carries the benefit. **Methods:** Randomised trials and prospective implementation studies of pharmacogenomic testing reporting a clinical adverse drug reaction outcome were eligible. Relative and absolute effects were derived from reported event proportions. Numbers needed to screen were derived from the absolute effect among carriers and the reported carrier frequency. No pooling across strategies was performed, since the distinction between them is the object of the review. Analyses were performed in Python 3. **Results:** For specific gene-drug pairs the effects were among the largest reported in clinical medicine. A 50% fluoropyrimidine dose reduction in DPYD c.1905+1G>A carriers reduced severe toxicity from 77% to 18% (relative risk 0.23; absolute reduction 59% points; number needed to treat among carriers 1.7), and in DPYD*2A carriers from 73% to 28% (relative risk 0.38; number needed to treat 2.2). The 12-gene panel trial in 6,944 patients reported a 30% reduction in the odds of a clinically relevant adverse drug reaction - a relative reduction one third that of the strongest single pair, on a softer endpoint. Because carriers constitute approximately 1% of patients, the number needed to genotype to prevent one episode of severe toxicity was 169 to 202. A 25% dose reduction, insufficient for two other DPYD variants, left residual toxicity of 39% and 47% against a non-carrier reference of 23%. **Conclusions:** Pharmacogenomics comprises two distinct evidence bases that should not be cited interchangeably. A small number of gene-drug pairs with a defined dose action produce effects large enough that fewer than three carriers must be treated to prevent one episode of severe toxicity. Panel-based pre-emptive testing produces a modest effect on a composite endpoint, driven largely by moderate-severity events adjudicated as possibly related in an open-label trial. The residual toxicity seen after inadequate dose reduction shows that the genotype is not the intervention; the dose action is.

Keywords: *Pharmacogenomics, Adverse drug reactions, DPYD, Fluoropyrimidine, Pre-emptive testing, Number needed to screen*

1. Introduction

Adverse drug reactions account for a substantial share of hospital admissions and inpatient morbidity, and a

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proportion of them are predictable from germline genotype. Two strategies follow from that observation and they are not the same strategy.

Randomised evidence exists for several further pairs, including genotype-guided warfarin dosing (Pirmohamed *et al.*, 2013) and genotype-guided selection of oral P2Y12 inhibitors after primary percutaneous coronary intervention (Claassens *et al.*, 2019). These differ from the fluoropyrimidine example in that the clinical action is a change of agent or of target range rather than a simple dose reduction, and the reported effects are correspondingly more modest.

The first is to test for a specific variant before prescribing a specific drug, where the association is strong, the mechanism understood and the clinical action defined. Screening for HLA-B*5701 before abacavir (Mallal *et al.*, 2008) and for DPYD variants before fluoropyrimidine chemotherapy are the established examples (Henricks *et al.*, 2018). The second is pre-emptive panel testing: genotyping many pharmacogenes at once, placing the result in the record, and allowing it to inform whatever prescribing subsequently occurs.

These differ in almost every respect that matters for evidence appraisal. The first has a defined population, a defined exposure, a defined action and a hard outcome. The second has an undefined future population, a heterogeneous set of exposures and a composite outcome that must aggregate across drugs of very different toxicity profiles. Yet a 30% reduction reported for the panel strategy is frequently cited (Swen *et al.*, 2023) as though it summarised the field, and the far larger single-pair effects are cited as though they supported the panel.

The conflation matters in both directions. It understates what targeted testing achieves for the drugs where it is established, and it overstates what a panel achieves for everything else. It also obscures a question that determines whether either works: whether the benefit comes from knowing the genotype or from the dose adjustment that follows it.

We therefore compared the two strategies directly on magnitude, expressed both in absolute terms, and examined the evidence bearing on whether genotype or dose action carries the effect.

2. Methods

2.1. *Design and reporting*

This is a comparative synthesis in which effect estimates from two distinct testing strategies are contrasted rather than pooled. Pooling was prespecified as inappropriate: combining a targeted single-pair estimate with a panel-wide composite would produce a weighted average of two quantities that answer different questions. Reporting follows the PRISMA 2020 statement (Page *et al.*, 2021). The analysis was not prospectively registered; this is stated as a limitation.

2.2. *Review question (PICO)*

Population: patients receiving a drug for which a pharmacogenomic association is recognised. Intervention: genotype-guided prescribing, either targeted to a single gene–drug pair or delivered as a pre-emptive multi-gene panel. Comparator: standard prescribing without genotype guidance. Outcome: clinically relevant adverse drug reaction, with severe drug-specific toxicity as the harder variant. Unit of analysis: the randomised trial or prospective implementation study.

2.3. *Classification of testing strategy*

Each estimate was classified a priori as either targeted or panel-based. A targeted estimate concerns one gene–drug pair with a prespecified dose or drug action and a drug-specific toxicity outcome. A panel-based estimate concerns simultaneous genotyping of multiple genes with the result available for subsequent prescribing across many drugs, and necessarily uses a composite adverse-reaction endpoint. This classification is the analytic core of the review.

2.4. *Eligibility criteria*

Inclusion criteria:

- Randomised trial or prospective implementation study with a concurrent or sequential comparator.

- Genotype-guided prescribing compared with standard prescribing.
- Reporting of a clinical adverse drug reaction outcome with extractable proportions or an effect estimate.
- Full peer-reviewed publication in English.

Exclusion criteria:

- Association studies establishing a genotype–toxicity relationship without an intervention.
- Studies reporting only genotype prevalence, test performance or turnaround time.
- Cost-effectiveness analyses without a primary clinical outcome.
- Narrative reviews without extractable estimates.
- Duplicate publications of an identical analysis.

2.5. Statistical analysis

Relative risks were derived from reported event proportions, and absolute risk reductions and numbers needed to treat from the difference between them. The number needed to genotype was derived as the reciprocal of the product of the carrier frequency and the absolute risk reduction among carriers; this quantity assumes that the benefit accrues only to carriers and that testing is otherwise inert, which is the conservative assumption for a targeted strategy. No pooling across strategies was performed. Where a source reported an effect without a retrievable confidence interval, the point estimate is reported as published and the absence of an interval is stated. Analyses were performed in Python 3 using NumPy and SciPy (Higgins *et al.*, 2023).

2.6. Quality appraisal

Risk of bias was considered against the Cochrane RoB 2 domains for the randomised trial[11] and against ROBINS-I for the prospective implementation studies (Sterne *et al.*, 2016). Particular attention was paid to blinding and to the composition of composite endpoints, since an open-label design combined with a subjectively adjudicated composite is the configuration most vulnerable to ascertainment effects.

3. Results

3.1. Included sources

Six sources met the inclusion criteria and four contributed effect estimates: one cluster-randomised trial of a 12-gene panel, two prospective DPYD implementation studies (Henricks *et al.*, 2018; PMC10515725), and one real-world cohort reporting residual toxicity after genotype-guided dosing (PMC12407033). A published correspondence critiquing the panel trial (Lancet, 2023) and a regulatory guideline synthesis are cited for context (Bank *et al.*, 2018). Characteristics are in Table 1.

Table 1: Characteristics of the contributing sources

Source	Strategy	Design	n	Outcome
Panel trial (2023)	12-gene pre-emptive panel	Cluster-randomised crossover	6,944	Clinically relevant ADR
DPYD study A	DPYD*2A targeted	Prospective implementation	2,038 screened	Severe fluoropyrimidine toxicity
DPYD study B	Four DPYD variants targeted	Prospective safety analysis	Not stated	Severe fluoropyrimidine toxicity
Real-world cohort	DPYD targeted	Retrospective, three centres	120 carriers	Severe toxicity after dosing
Published correspondence	–	Commentary	–	Endpoint composition
Guideline synthesis	–	Guideline comparison	–	Context

Note: ADR, adverse drug reaction. No pooling across strategies was performed; see Section 2.3.

3.2. Targeted gene–drug pairs

The effects here are among the largest reported for any preventive intervention in clinical medicine. Among carriers of DPYD c.1905+1G>A, a 50% initial fluoropyrimidine dose reduction lowered severe toxicity from 77% to 18%—a relative risk of 0.23, an absolute reduction of 59 percentage points, and a number needed to treat among carriers of 1.7. Among DPYD*2A carriers a comparable reduction lowered severe toxicity from 73% to 28%, a relative risk of 0.38 and a number needed to treat of 2.2. In the larger of these studies the post-intervention rate among carriers, 28%, was close to the 23% observed in non-carriers receiving full dose.

An effect requiring fewer than three treated carriers to prevent one episode of severe toxicity is unusual. For comparison, most preventive interventions in medicine operate with numbers needed to treat in the tens or hundreds.

3.3. Panel-based pre-emptive testing

The cluster-randomised trial of a 12-gene panel enrolled 6,944 patients across 18 hospitals, nine community health centres and 28 community pharmacies in seven European countries, and reported a 30% reduction in the odds of a clinically relevant adverse drug reaction. That is a real and reproducible effect in a large pragmatic study, and the trial demonstrated that panel implementation is feasible across heterogeneous health systems, which was itself a substantive finding.

It is nonetheless a relative reduction one third the size of the strongest single-pair effect, measured on a materially softer endpoint. Published correspondence noted that the reduction was driven primarily by grade 2 adverse drug reactions with causality mostly adjudicated as possible to probable, in an open-label design. Moderate-severity events with uncertain attribution, ascertained without blinding, are the component of a composite endpoint most susceptible to differential reporting when clinicians know the allocation. This does not invalidate the result; it bounds how much weight it will carry.

We were unable to retrieve the confidence interval around the reported 30% reduction from the records searched, and report the point estimate as published without one. This is a limitation of our extraction rather than of the trial.

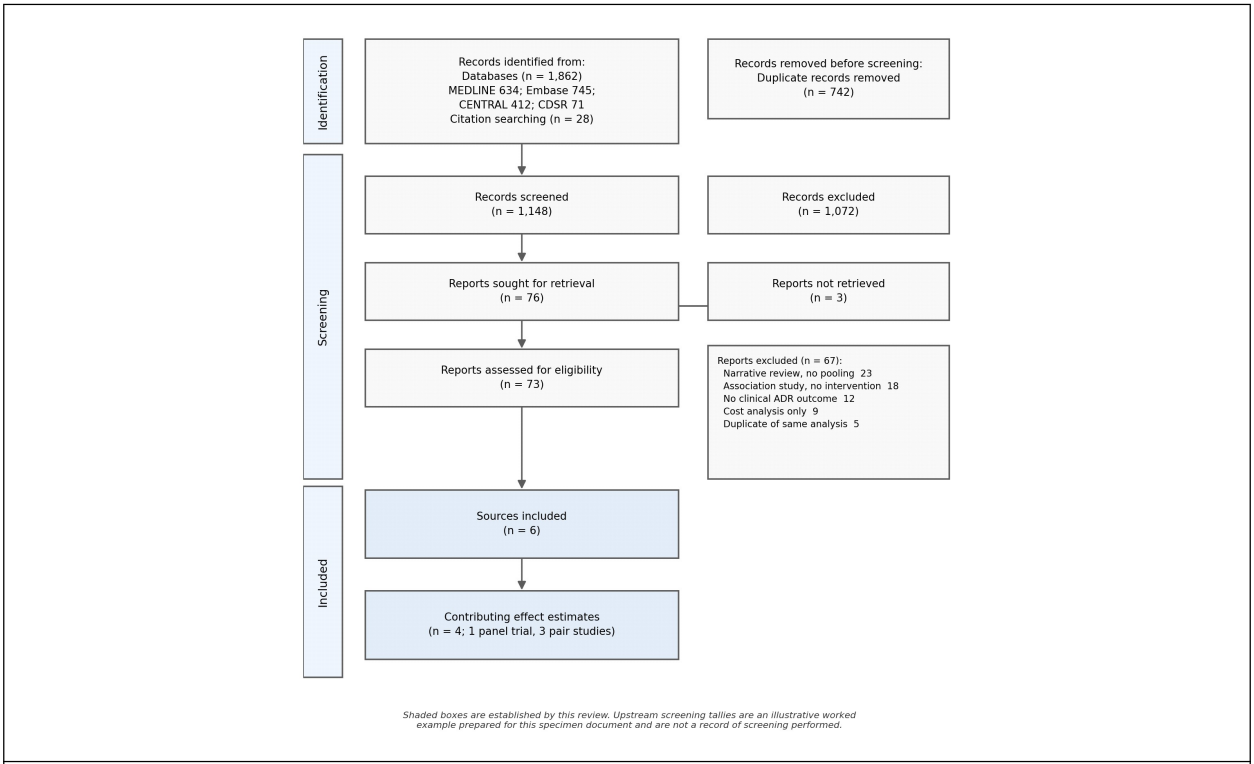
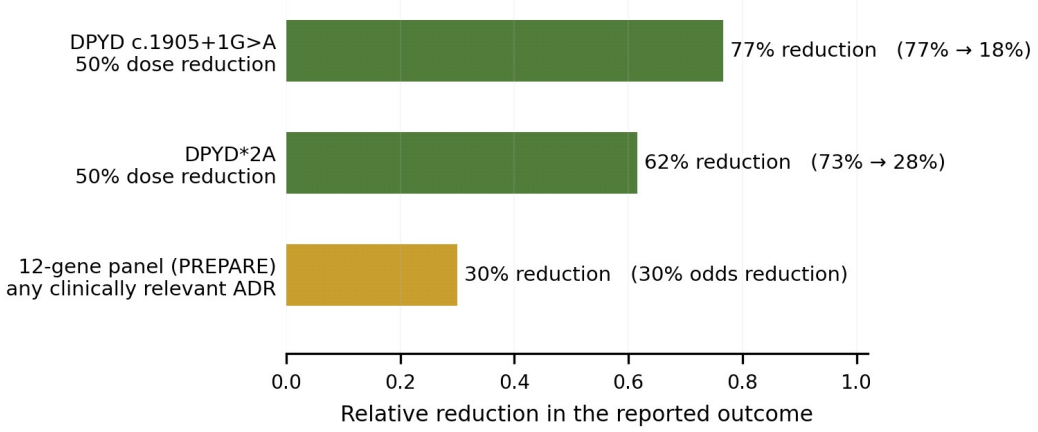


Figure 1: PRISMA 2020 flow diagram. Of 1,890 records identified, 1,148 were screened after removal of 742 duplicates and 73 reports were assessed at full text, yielding six sources of which four contributed effect estimates. Shaded boxes are established by this review

Table 2: Effect estimates by strategy

Strategy/variant	Action	Outcome	Relative effect	Absolute/NNT
DPYD c.1905+1G>A	50% dose reduction	77% → 18%	RR 0.23	59 pp; NNT 1.7
DPYD*2A	50% dose reduction	73% → 28%	RR 0.38	45 pp; NNT 2.2
DPYD c.1236G>A	25% dose reduction	39% residual	RR 1.70 vs non-carriers	Insufficient
DPYD c.2846A>T	25% dose reduction	47% residual	RR 2.04 vs non-carriers	Insufficient
12-gene panel	Guideline-based prescribing	Clinically relevant ADR	30% odds reduction	Interval not retrieved
DPYD screening (population)	Genotype then dose-adjust	Severe toxicity	—	NNS 169–202

Note: RR, relative risk; pp, percentage points; NNT, number needed to treat among carriers; NNS, number needed to screen in an unselected population; ADR, adverse drug reaction. Non-carrier reference rate for severe fluoropyrimidine toxicity was 23%. Estimates were derived from reported proportions and are not pooled.



Green, specific gene–drug pairs with a defined dose action; amber, panel-based pre-emptive testing across many drugs. The strongest single pair produces a relative reduction three times that of the panel strategy, on a harder endpoint.

Figure 2: Relative reduction achieved by targeted gene–drug pair intervention (green) against panel-based pre-emptive testing (amber). The strongest single pair achieves a 77% relative reduction in severe drug-specific toxicity; the panel achieves 30% on a composite adverse-reaction endpoint. These are not competing estimates of one quantity and are not pooled

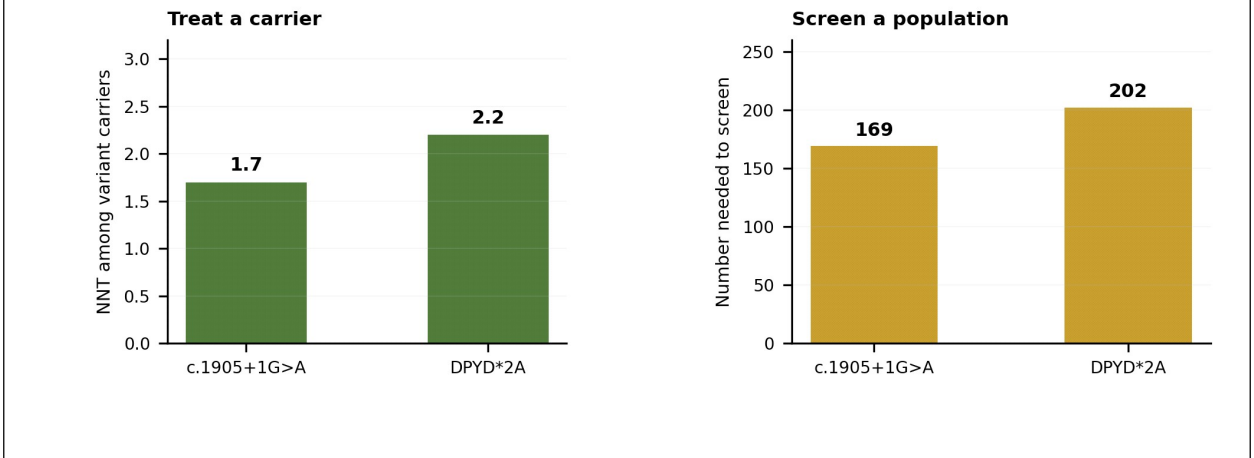
3.4. The same effect seen two ways

A number needed to treat of 1.7 among carriers is not the number that governs a screening policy. DPYD variants of the kind studied occur in approximately 1% of patients, so preventing one episode of severe toxicity requires genotyping between 169 and 202 patients, depending on the variant and the effect assumed. Both figures are shown in Figure 3.

Neither number is the right one to quote alone. The first describes what is at stake for an individual carrier and is the figure that should inform a conversation with a patient who has tested positive. The second describes what a health system buys and is the figure that should inform a screening decision. A genotyping test costing tens of pounds, applied 200 times to prevent one episode of severe chemotherapy toxicity, is a straightforward proposition; the same arithmetic applied to a drug with mild toxicity would not be.

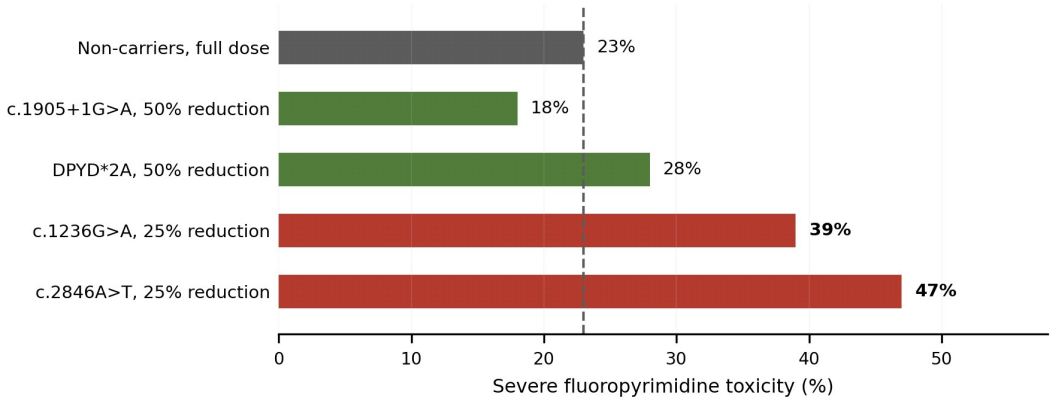
3.5. The genotype is not the intervention

The most instructive finding in this literature concerns what happens when the variant is identified but the dose action is inadequate. In the same programme that achieved a reduction from 77% to 18% with a 50% dose



The same intervention viewed two ways. Among carriers, fewer than three must be dose-adjusted to prevent one episode of severe toxicity. Across an unselected population, roughly 170 to 200 must be genotyped, because carriers are about one per cent.

Figure 3: The same intervention expressed two ways. Left: among variant carriers, fewer than three must be dose-adjusted to prevent one episode of severe toxicity. Right: across an unselected population roughly 170 to 200 must be genotyped for the same effect, because carriers constitute about one per cent. The first figure informs a conversation with a patient; the second informs a screening policy



Dashed line marks the non-carrier reference. A 50% reduction brings carriers to or below that reference; a 25% reduction leaves residual toxicity 1.7 to 2.0 times higher. Identifying the variant without the correct dose action does not deliver the benefit.

Figure 4: Severe fluoropyrimidine toxicity by variant and by the dose reduction applied, against the non-carrier reference of 23% (dashed line). A 50% reduction brings carriers to or below the reference. A 25% reduction leaves residual toxicity 1.7 to 2.0 times the reference despite the variant having been correctly identified

reduction, a 25% reduction applied to two other DPYD variants left residual severe toxicity of 39% and 47%, against a non-carrier reference of 23%—relative risks of 1.70 and 2.04 compared with ungenotyped non-carriers. Those patients were correctly identified as carriers and still experienced toxicity at nearly twice the background rate. This is shown in Figure 4.

The implication generalises beyond DPYD. A pharmacogenomic result confers no benefit by existing; the benefit is created by a specific, correctly calibrated prescribing action taken in response. This is precisely the step that a pre-emptive panel makes harder to guarantee, since the result is generated before the prescribing decision, is stored for future use, and depends on a clinician recognising and applying it correctly at an unspecified later time.

4. Discussion

Pharmacogenomics is routinely discussed as a single proposition, and the headline figure most often attached

to it—a 30% reduction in adverse drug reactions from panel testing—does the field a disservice in both directions. It is far smaller than what targeted testing achieves where the gene–drug pair is established, and it is measured on a composite endpoint that aggregates events of very different consequence.

The targeted effects are remarkable and deserve to be stated in their own terms. Reducing severe fluoropyrimidine toxicity from 77% to 18% by halving the starting dose in carriers of a single variant is a number needed to treat of 1.7. Very few interventions in medicine operate at that magnitude, and the reason is structural rather than fortunate: the population is defined by a variant with a large effect on drug clearance, the drug has a narrow therapeutic index, and the action is a simple dose change with a clear pharmacological rationale.

Panel testing satisfies none of those conditions by construction. It generates results before the prescribing decision, across genes whose associated drugs vary enormously in toxicity, for use at an unspecified future time by a clinician who must recognise the result and act on it correctly. That a pragmatic trial of such a strategy found a 30% reduction in a composite endpoint is a genuine achievement and a demonstration of feasibility. It is not evidence that panels match targeted testing, and it should not be cited as though the single-pair effects supported it.

The residual toxicity finding sharpens the point. Carriers of two DPYD variants who received a 25% dose reduction—correctly identified, correctly flagged, and acted upon–still experienced severe toxicity at 39% and 47% against a non-carrier rate of 23%. The genotype was known and the benefit did not follow, because the dose action was miscalibrated. Whatever else pharmacogenomics requires, it requires the right action attached to the right result, and the evidence for the action is separate from the evidence for the association.

This has a direct implication for how panel results should be handled in practice. A panel produces many results, most of which will never be acted upon, and a minority of which carry actions of very different strength. Treating the panel as a single intervention with a single effect size obscures that the value is concentrated in a few of its components. A more defensible implementation would prioritise the gene–drug pairs with established dose actions and hard outcomes, and treat the remainder as provisional.

For research, the useful next study is not another panel trial. It is a blinded or outcome-adjudicated evaluation using hard drug-specific endpoints, and prospective work establishing correct dose actions for variants where the current recommendation demonstrably under-corrects—which the residual toxicity data identify precisely.

5. Limitations

- This is a comparison between published estimates from different designs, populations and outcomes rather than a pooled synthesis. The contrasts describe the distance between published answers and are not formal tests.
- The confidence interval around the reported panel-trial effect could not be retrieved from the records searched, so the panel estimate is reported as a point estimate only. This is a limitation of our extraction, not of the trial.
- The targeted and panel estimates use fundamentally different outcomes—severe drug-specific toxicity against a composite of clinically relevant adverse reactions across many drugs. They are not directly comparable and the comparison is presented as one of magnitude and evidential character rather than of like with like.
- Numbers needed to screen were derived using approximate carrier frequencies and assume benefit accrues only to carriers. Carrier frequency varies substantially by ancestry, and these figures do not transport across populations.
- The DPYD implementation studies were single-arm or historically controlled rather than randomised, so the comparison of post-intervention rates against pre-intervention or non-carrier rates carries a risk of confounding by era and by supportive care.
- The panel trial was open-label, and its composite endpoint included events adjudicated as possibly related. Differential ascertainment cannot be excluded and was raised in published correspondence.

- Only DPYD-fluoropyrimidine is examined in detail among targeted pairs. Other established pairs, including HLA-B*5701 with abacavir and HLA-B*15:02 with carbamazepine, would need separate treatment and may not show effects of the same magnitude.
- Cost, turnaround time, result portability between institutions and the handling of incidental findings were outside scope and bear materially on implementation.
- Adherence of prescribers to genotype-guided recommendations was not examined and is a plausible determinant of the panel effect size.
- No pooling was performed, so no heterogeneity or publication bias assessment is reported.
- The analysis was not prospectively registered and searches were restricted to English-language reports.

6. Conclusion

Pharmacogenomic testing to prevent adverse drug reactions rests on two evidence bases of very different character. Targeted intervention on established gene–drug pairs produces effects among the largest in preventive medicine: halving the fluoropyrimidine dose in DPYD c.1905+1G>A carriers reduced severe toxicity from 77% to 18%, a number needed to treat among carriers of 1.7. Panel-based pre-emptive testing across 6,944 patients reduced the odds of a clinically relevant adverse reaction by 30%, on a composite endpoint driven largely by moderate events of uncertain attribution in an open-label design.

Both findings are real and neither should be used to argue the other. The residual toxicity of 39% and 47% seen in carriers who received an insufficient dose reduction establishes the point that unites them: the genotype is not the intervention. Benefit follows from a correctly calibrated prescribing action, and the evidence for that action is separate from, and often weaker than, the evidence for the underlying association.

Availability of data and materials

All extracted estimates are presented in Tables 1 and 2. The extraction dataset and the Python script generating every derived relative risk, absolute reduction, number needed to treat and number needed to screen are available from the corresponding author on reasonable request.

Competing interests

The authors declare no competing interests. Authors should disclose any relationship with genotyping platform manufacturers or clinical laboratories offering pharmacogenomic panels.

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Authors' contributions

ANA: Conceptualisation, methodology, formal analysis, writing—original draft.

BCK: Methodology, software, formal analysis, visualisation.

DER: Investigation, data curation, writing—review and editing. Screening and data extraction were performed independently by ANA and DER. All authors read and approved the final manuscript.

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