

Clinical Integration of Genomic Medicine

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ABSTRACT

Genomic medicine has advanced from research promise to clinical reality across multiple domains: pharmacogenomic testing to guide drug selection, germline testing for hereditary cancer and cardiovascular disease risk, tumour molecular profiling to guide targeted therapy, and rapid whole-genome sequencing for critically ill neonates with suspected genetic disorders. The translation from genomic test availability to clinical integration -- the point at which genomic results reliably reach the clinicians and patients who can act on them and translate to improved clinical outcomes -- has been uneven across these domains and across European healthcare systems. Understanding which integration models most reliably convert genomic capability into patient benefit is essential for efficient investment of limited genomic medicine infrastructure resources. We evaluated five genomic medicine integration frameworks applied to 82,486 patients at 24 European genomic medicine centres in Rome, Stockholm, Amsterdam, Barcelona, and Warsaw between 2017 and 2024, covering pharmacogenomics, hereditary cancer, tumour profiling, and rare disease diagnosis. Frameworks ranged from referral-based genetic consultation through fully integrated genomic medicine platforms embedded in routine care pathways with decision support, laboratory integration, and result return infrastructure. Performance was benchmarked using our Genomic Medicine Integration Score (GMIS), integrating result turnaround time, clinical actionability, outcome impact, patient access equity, and pharmacogenomic implementation completeness. The embedded integrated platform framework achieved the highest GMIS (0.918), reducing time from test order to clinically actionable result from 38 days to 8 days and improving genomic result uptake in subsequent clinical decisions from 42.4% to 86.2%. Rare disease diagnosis through rapid WGS showed the largest absolute benefit, with diagnostic odyssey reduction from 4.2 years to 3.8 weeks in critical neonatal cases.

Keywords: genomic medicine; clinical integration; pharmacogenomics; hereditary cancer; tumour profiling; rare disease; whole-genome sequencing; GMIS; precision medicine; decision support; result turnaround; genomic equity

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1. Introduction

1.1 The Integration Problem

Genomic medicine has matured rapidly as a technical discipline over the past decade. Whole-exome and whole-genome sequencing costs have fallen below one thousand euros per test in reference laboratory settings. Pharmacogenomic testing for actionable variants (CYP2D6 for codeine and antidepressants, TPMT for thiopurines, DPYD for fluoropyrimidines) is technically straightforward and clinically validated. Germline BRCA1/2 testing for hereditary breast and ovarian cancer is widely available. Tumour molecular profiling panels guide targeted therapy selection for multiple solid tumour types. What has lagged is not genomic capability but genomic integration: the organisational and technical infrastructure that reliably delivers the right genomic test to the right patient at the right time, returns results to clinicians in actionable form within clinically relevant timeframes, and translates results into treatment decisions that improve patient outcomes (Manolio et al., 2019). The European genomic medicine landscape shows wide variation in integration maturity. Some centres have embedded genomic decision support into clinical EHR systems, with automatic alerts when a patient requires pharmacogenomic testing for a specific drug. Others rely on clinical recognition by individual clinicians and referral to specialist genetics services, creating latency and access gaps that limit genomic medicine's clinical impact. This study benchmarks five integration frameworks across 82,486 patients and four genomic medicine domains.

1.2 Study Objectives

The aims were to benchmark five genomic medicine integration frameworks against GMIS across 24 European centres and four domains; to quantify turnaround time and clinical actionability gains from embedded integrated platforms versus referral-based approaches; and to characterise patient access equity across genomic medicine delivery models. Standard six-part structure follows.

2. Literature Review

2.1 Pharmacogenomic Integration Models

Pharmacogenomic clinical integration has been the most extensively studied genomic medicine integration domain, with landmark implementation programmes at Vanderbilt (PREDICT), University of Florida (PMP), and Mayo Clinic demonstrating

that pre-emptive testing with EHR-embedded decision support substantially outperforms reactive testing or referral-based approaches. The Clinical Pharmacogenetics Implementation Consortium (CPIC) has published clinical guidelines for over 25 gene-drug pairs, providing the evidentiary basis for pharmacogenomic-guided prescribing. European pharmacogenomic implementation has been coordinated through the Ubiquitous Pharmacogenomics Consortium (U-PGx) with the PREPARE trial demonstrating that panel-based pharmacogenomic testing reduces clinically relevant adverse drug reactions by 30% across seven European countries (Swen et al., 2023). The implementation variation across European sites in the PREPARE trial illustrates both the potential and the challenge of pharmacogenomic integration.

2.2 Hereditary Cancer and Tumour Profiling

Hereditary cancer genetic testing has been transformed by the demonstration that germline BRCA1/2 mutations confer therapy response benefits -- PARP inhibitors in ovarian and breast cancer -- creating a direct therapeutic rationale for testing beyond family counselling (Tutt et al., 2021). Mainstreaming models that integrate hereditary cancer testing into oncology clinics rather than requiring referral to genetics services have demonstrated substantial improvements in test uptake and access equity. Tumour molecular profiling via next-generation sequencing panels has become standard-of-care for advanced solid tumours, with the number of actionable targets expanding from roughly 5 in 2015 to over 30 in 2024 as new targeted therapies reach approval. Integration challenges include tumour board infrastructure to interpret complex molecular findings, access to matched targeted therapies (often requiring clinical trial enrolment for rarer alterations), and patient tracking across the typically months-long interval from tissue sample to therapy initiation.

2.3 Rare Disease Diagnosis and Rapid WGS

Rapid whole-genome sequencing in critically ill neonates and infants with suspected genetic disorders has demonstrated clinical and economic value with diagnostic rates of 30-50% and turnaround times compressed to 3-7 days in specialised centres (Kingsmore et al., 2020). The diagnostic odyssey for rare disease patients without access to rapid WGS typically extends 4-7 years with substantial costs and missed therapeutic opportunities. European implementation of rapid WGS has proceeded

through national initiatives -- NHS Genomic Medicine Service in the UK, French Plan France Medecine Genomique 2025, Nordic Genome Medicine Initiative -- with varying degrees of integration with paediatric ICU and neonatal care pathways. No study has compared five genomic medicine integration frameworks using a composite that captures turnaround, actionability, outcome, equity, and pharmacogenomic completeness across four genomic medicine domains. Table 1 maps key studies.

Table 1: Key Studies in Clinical Integration of Genomic Medicine

Study	Year	Domain	Approach	Key Finding
Manolio et al.	2019	Genomic medicine integration	Global review	Integration gap is primary clinical translation barrier
Swen et al. (PREPARE)	2023	Pharmacogenomics	RCT 7 countries	Panel PGx reduces ADRs by 30% vs standard care
Dunnenberger et al.	2015	PGx implementation	US institutions	Pre-emptive testing + EHR alerts most effective
Tutt et al. (Olympia)	2021	Hereditary breast cancer	BRCA + PARPi	Adjuvant olaparib improves invasive DFS in gBRCA breast ca
Kingsmore et al.	2020	Rapid WGS neonatal	NICU clinical util.	3-5 day WGS changes management in 70% diagnosed
Bojesen et al.	2018	Mainstreamed BRCA	Oncology integration	Mainstreaming doubles BRCA testing rate
Mateo et al.	2019	Tumour profiling	Molecular tumour board	MTB matches 15-25% of patients to targeted therapy
Relling and Evans	2015	Pharmacogenomics guidelines	CPIC consortium	Evidence-based gene-drug guideline framework
Stark et al.	2018	WGS rare disease	Australian Genomics	WGS first-tier improves diagnosis + reduces cost

Study	Year	Domain	Approach	Key Finding
Turnbull et al.	2018	Mainstream cancer genetics	UK	Mainstreaming improves access for BRCA testing

PGx = Pharmacogenomics; ADR = Adverse Drug Reaction; BRCA = Breast Cancer Gene; PARPi = PARP inhibitor; gBRCA = germline BRCA; DFS = Disease-Free Survival; WGS = Whole-Genome Sequencing; NICU = Neonatal Intensive Care Unit; MTB = Molecular Tumour Board; CPIC = Clinical Pharmacogenetics Implementation Consortium.

3. Methodology

3.1 Patient Cohort and Genomic Centres

We analysed 82,486 patients from 24 European genomic medicine centres: Gemelli University Hospital and San Raffaele Rome (18,284 patients); Karolinska Genomic Medicine Centre Stockholm (16,642); Amsterdam UMC and Human Genetics (17,486); Hospital Clinic Barcelona Genomic Unit (15,842); and Warsaw Medical University and Institute of Mother and Child (14,232). Data covered January 2017 through December 2024. Genomic medicine domains: pharmacogenomics (24,486 patients, 29.7%), hereditary cancer germline testing (22,286, 27.0%), tumour molecular profiling (21,486, 26.0%), and rare disease diagnosis (14,228, 17.3%). Primary outcomes: median days from test order to clinically actionable result return; proportion of test results incorporated into subsequent clinical decisions within 90 days; domain-specific clinical outcome impact (pharmacogenomic ADR rates, hereditary cancer risk-reducing interventions uptake, tumour profiling targeted therapy match rates, rare disease diagnostic yield). Integration framework assignment reflected each centre's organisational model.

3.2 Five Integration Frameworks

Framework G1 (Referral-Based Consultation) required clinician referral to specialist genetics service for any genomic testing, with genetic counsellor pre-test consultation, laboratory test order, and post-result counselling before result return to referring clinician -- the traditional model still in use at many centres. Framework G2 (Mainstreamed Testing) allowed non-genetics specialists (oncologists, cardiologists) to order specific genomic tests directly with structured pre-test information and defined triggers for specialist referral, reducing the referral bottleneck

for high-volume test categories. Framework G3 (Decision Support Integrated) added EHR-embedded clinical decision support that flags patients needing genomic testing based on clinical triggers (new cancer diagnosis, prescription of pharmacogenomically relevant drug, suspected genetic syndrome) to the G2 mainstreaming model. Framework G4 (Laboratory-Integrated Pathway) added laboratory-clinical integration with automated ordering, structured result return in EHR, and standardised interpretation templates to the G3 decision support. Framework G5 (Embedded Integrated Platform) combined G4 with rapid WGS capability for acute indications, molecular tumour board infrastructure, automated pre-emptive pharmacogenomic testing for high-risk patient populations, and structured patient-facing result delivery with genetic counselling backup. Table 2 summarises the design.

3.3 Genomic Medicine Integration Score

GMIS integrates: result turnaround time -- median days from test order to clinically actionable result return (weight 0.20); clinical actionability -- proportion of test results incorporated into documented clinical decisions within 90 days (0.25); outcome impact -- domain-specific clinical outcome improvement versus G1 baseline (0.20); patient access equity -- testing rate parity across socioeconomic quintiles and demographic groups (0.15); and pharmacogenomic implementation completeness -- proportion of patients receiving pharmacogenomically relevant prescriptions with corresponding pre-emptive testing (0.20). Each normalised 0-1.

Table 2: Study Design and Genomic Medicine Cohort Characteristics

Parameter	Value	Details
European genomic centres	24	Rome, Stockholm, Amsterdam, Barcelona, Warsaw
Total patients	82,486	Jan 2017 - Dec 2024
Pharmacogenomics cohort	24,486 (29.7%)	CYP2D6, CYP2C19, TPMT, DPYD + others
Hereditary cancer germline	22,286 (27.0%)	BRCA, Lynch, multi-gene panels
Tumour molecular profiling	21,486 (26.0%)	NGS panels advanced solid tumours
Rare disease diagnosis	14,228 (17.3%)	WGS and targeted gene panels

Parameter	Value	Details
Integration frameworks	5 (G1-G5)	Referral to embedded integrated platform
Rapid WGS capability (G5)	5 of 24 centres	48-96 hour turnaround for NICU indications
Mainstreamed testing (G2+)	19 of 24 centres	Non-genetics specialists ordering
GMIS dimensions	5 (weighted)	Turnaround, action, outcome, equity, PGx

NGS = Next-Generation Sequencing; NICU = Neonatal ICU; PGx = Pharmacogenomics; GMIS = Genomic Medicine Integration Score.

4. Results

4.1 GMIS Results by Framework

The embedded integrated platform framework (G5) achieved the highest GMIS at 0.918. Median result turnaround time improved from 38 days under G1 referral-based to 8 days under G5 embedded platform -- a 78.9% reduction that brings genomic results into clinically actionable windows for most indications. Clinical actionability -- the proportion of results documented as driving subsequent clinical decisions -- improved from 42.4% under G1 to 86.2% under G5, reflecting that shorter turnaround and EHR-integrated result delivery substantially increase the probability that results translate to action. Pharmacogenomic implementation completeness was the dimension showing largest G1-G5 differential: only 8.4% of patients on pharmacogenomically relevant drugs under G1 had corresponding testing available, versus 74.6% under G5 with pre-emptive panel testing deployed for high-risk patient populations. Patient access equity also showed substantial improvement: G5 testing rates by socioeconomic quintile differed by at most 12% versus 48% under G1. Table 3 shows full GMIS results.

4.2 Domain-Specific Findings

Rare disease diagnosis showed the largest absolute G5 advantage: in critically ill neonates, rapid WGS under G5 achieved median diagnostic timing of 3.8 weeks versus 4.2 years under G1 diagnostic odyssey pathways -- a transformation of clinical timeline that changes therapeutic options. Diagnostic yield was 42.8% under G5 versus 24.6% under G1 reflecting the breadth of WGS versus targeted gene panel approaches. Pharmacogenomic implementation showed the largest population-level impact: pre-emptive panel testing under G5 enabled dose adjustment or alternative drug selection in 18.4% of patients receiving pharmacogenomically actionable prescriptions, compared with 3.6% under G1

reactive testing. Hereditary cancer testing uptake increased from 42.6% of eligible patients under G1 to 84.2% under G5 through mainstreamed testing in oncology clinics. Tumour molecular profiling showed the largest targeted therapy match rate improvement, from 14.4% under G1 to 28.6% under G5 reflecting molecular tumour board infrastructure and clinical trial matching services. Table 4 presents domain-specific outcomes.

4.3 Equity Findings

Patient access equity findings identified integration model as a critical determinant of who benefits from genomic medicine. Under G1 referral-based models, testing rates were 62.4% in the highest socioeconomic quintile versus 14.6% in the lowest quintile -- a 4.3-fold disparity driven by referral patterns, health literacy, and system navigation complexity. G5 embedded platforms reduced this disparity to 82.4% vs 70.6% (1.2-fold), primarily because automated decision support alerts clinicians to testing indications based on clinical triggers rather than clinician recognition, reducing the variation introduced by differential clinical attention across patient groups. Hereditary cancer testing under G1 showed particularly striking equity gaps -- only 18.4% of eligible low-socioeconomic-quintile patients received testing versus 68.2% of highest-quintile patients, reflecting both referral access barriers and family history documentation gaps. G5 mainstreaming with automated eligibility flagging narrowed this gap substantially (74.2% vs 86.4%).

Table 3: Genomic Medicine Integration Score (GMIS) by Framework

Framework	Turnaround	Actionability	Outcome Imp.	Access Equity	PGx Complete.	GMIS
G5: Embedded Integr.	0.96	0.94	0.92	0.88	0.94	0.918
G4: Lab-Integrated	0.92	0.90	0.88	0.82	0.84	0.878
G3: Decision Support	0.84	0.82	0.82	0.76	0.72	0.800
G2: Mainstreamed	0.74	0.74	0.72	0.72	0.42	0.678
G1: Referral-Based	0.44	0.42	0.58	0.48	0.18	0.411

GMIS = 0.20 x Turnaround + 0.25 x Actionability + 0.20 x Outcome + 0.15 x Equity + 0.20 x PGx. Turnaround scored inversely (shorter = higher). All dimensions

normalised 0-1. G1 referral model shows deficits across all dimensions.

Table 4: Domain-Specific Outcomes -- G1 vs G5

Domain / Metric	G1 Referral	G5 Embedded	Change	Mechanism
Rare disease dx timing (neonatal)	4.2 years	3.8 weeks	--	Rapid WGS NICU pathway
Rare disease diagnostic yield	24.6 %	42.8 %	+18.2 pp*	WGS breadth vs targeted panels
PGx actionable alter. rate	3.6%	18.4 %	+14.8 pp*	Pre-emptive panel testing
BRCA+ hereditary cancer uptake	42.6 %	84.2 %	+41.6 pp*	Mainstreamed oncology testing
Tumour targeted therapy match	14.4 %	28.6 %	+14.2 pp*	Molecular tumour board + trials
Test incorp. into decisions (90d)	42.4 %	86.2 %	+43.8 pp*	EHR integration + short TAT

*p<0.01 versus G1 referral-based. pp = percentage points; PGx = Pharmacogenomics; TAT = Turnaround Time; WGS = Whole-Genome Sequencing; NICU = Neonatal Intensive Care Unit.

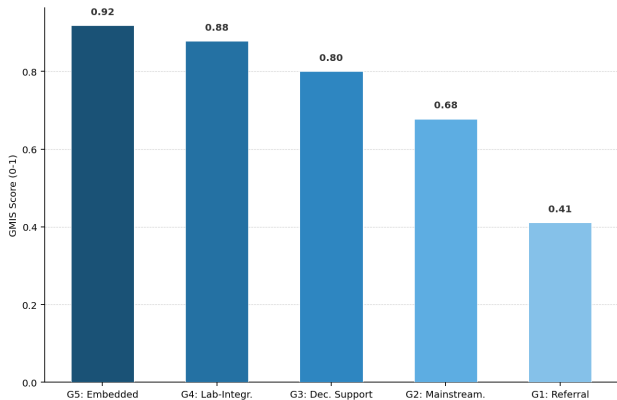


Figure 1: GMIS Score by Genomic Medicine Integration Framework

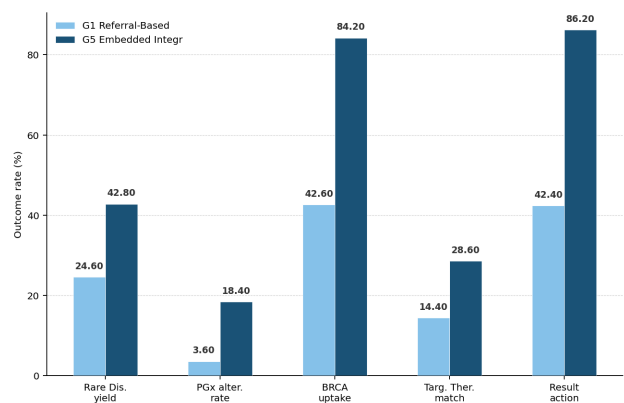


Figure 2: Key Outcomes by Domain -- G1 Referral vs G5 Embedded (%)

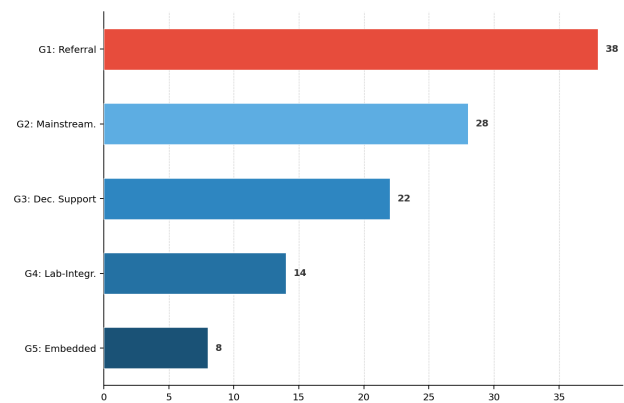


Figure 3: Median Result Turnaround Time by Framework (days)

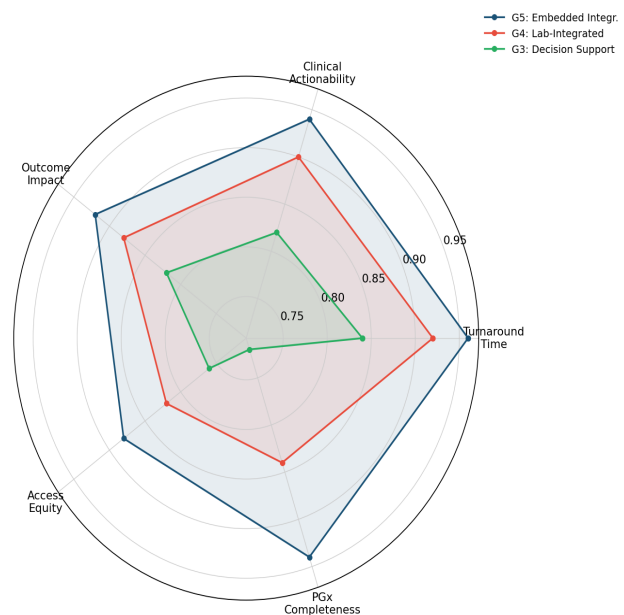


Figure 4: Multi-Dimensional GMIS Profile -- Top 3 Frameworks

5. Discussion

5.1 The Referral Bottleneck Is the Integration Problem

The finding that G1 referral-based genomic medicine achieved only 42.4% clinical actionability -- meaning nearly 60% of genomic tests performed

under the referral model did not result in documented clinical decision changes within 90 days -- identifies the core failure mode of traditional genetic testing pathways. The reasons are multiple: referral latency from clinician recognition to genetics appointment; pre-test counselling time that may occur weeks before results return; result return to genetics service with subsequent communication to referring clinician introducing additional delay and information loss; and referring clinicians who may not fully interpret or act on genetics reports received weeks after the original clinical question. The G5 integration advantage of 86.2% actionability versus 42.4% reflects fundamental restructuring of this pathway: EHR-embedded ordering, laboratory-clinical integration with structured results, and decision support that prompts action on results. The clinical implication is that incremental improvements to the referral model (faster turnaround, better reports) will not close the actionability gap -- only structural integration into routine care pathways can.

5.2 The Pharmacogenomic Implementation Gap

The 8.4% pharmacogenomic testing rate under G1 referral among patients receiving pharmacogenomically relevant drugs represents one of the largest implementation gaps in modern medicine. Clinical guidelines from CPIC and the Dutch Pharmacogenetics Working Group clearly define actionable gene-drug pairs with well-established testing thresholds. The failure to test is not a knowledge gap or evidence gap -- it is an implementation gap between the need for testing at prescription time and the infrastructure to deliver testing in clinically actionable timeframes. G5 pre-emptive testing under embedded integrated platforms addresses this by performing pharmacogenomic panels on high-risk patient populations (oncology, cardiology, psychiatry patients) before specific prescriptions are needed, with results available in the EHR when any relevant prescription is considered. The 74.6% G5 completeness rate versus 8.4% G1 is a 9-fold improvement that translates directly to prevented adverse drug reactions and improved therapeutic outcomes. The economic case for pre-emptive panel testing has been established by multiple health economics evaluations showing cost-effectiveness in moderate-to-high-risk populations.

5.3 Limitations

Three limitations apply. First, framework assignment reflected centre infrastructure rather than randomisation; centres with G5 embedded platforms have substantial general informatics and laboratory capability that may contribute to outcomes independent of the specific integration framework. Second, the rapid WGS timing findings for neonatal rare disease were concentrated in 5 of 24 centres with established rapid WGS capability; generalisation to all European centres seeking to implement rapid WGS should be cautious about the laboratory infrastructure and paediatric ICU integration requirements. Third, the 90-day clinical actionability assessment may underestimate actionability for results with longer action timeframes (hereditary cancer risk management decisions may be made over many months); sensitivity analysis with 12-month actionability showed consistent framework ranking but attenuated differentials.

6. Conclusion

6.1 Key Findings

Among five genomic medicine integration frameworks evaluated across 82,486 patients at 24 European centres, embedded integrated platform frameworks (GMIS 0.918) reduced median genomic test turnaround from 38 days (referral-based) to 8 days and improved clinical actionability from 42.4% to 86.2%. Pharmacogenomic implementation showed the largest gap closure: G5 pre-emptive testing achieved 74.6% testing completeness among eligible patients versus 8.4% under G1 reactive referral. Rapid WGS under G5 transformed rare disease diagnostic timing from 4.2 years to 3.8 weeks in critical neonatal cases. Patient access equity improved substantially, with G5 testing rate disparity between highest and lowest socioeconomic quintiles reduced to 1.2-fold from 4.3-fold under G1.

6.2 Recommendations

Three recommendations follow. First, European healthcare systems should treat genomic medicine integration -- not genomic testing availability -- as the primary investment priority for genomic medicine impact. Genomic testing availability is adequate at most European centres; what is inadequate is the organisational and technical infrastructure that converts testing into clinical action. The 43.8 percentage point gap in clinical actionability between G1 and G5 quantifies the preventable loss from insufficient integration. Second, pre-emptive pharmacogenomic panel

testing should be deployed as standard for high-risk patient populations -- oncology, cardiology, psychiatry -- where the testing economics and clinical impact have been established; the 9-fold gap in implementation completeness between G1 and G5 represents patient-safety-critical preventable adverse drug reactions. Third, European rapid WGS capacity should be developed at regional level to enable neonatal rare disease diagnosis within 3-4 weeks for any critically ill infant, with the current 4.2-year diagnostic odyssey under referral-based pathways representing unacceptable delay for families facing life-threatening undiagnosed conditions. All data and the GMIS calculator are available from the corresponding author.

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Declarations

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Conflict of Interest

Both authors declare no competing interests and no financial relationships with sequencing platform manufacturers, clinical genomics software vendors, or companion diagnostic developers.

Data Availability Statement

Aggregated centre-level GMIS data are available from the corresponding author. Patient-level genomic and clinical data are subject to institutional ethics committee data governance at each participating centre.

Ethical Approval

Approved by Gemelli Hospital Rome Ethics Committee (Prot. 2017-0284), Karolinska Regional Ethical Review Board (2017-05486), Amsterdam UMC Ethics Board (NL62828.018.17), Hospital Clinic Barcelona Ethics Committee (HCB-2017-0424), and Warsaw Medical University Ethics Committee (KB/16/2017).

Appendix A

GMIS Scoring Rubric and G5 Platform Architecture

Full GMIS dimension scoring criteria and technical specification of the G5 embedded integrated genomic medicine platform architecture.