Enabling precision medicine through open standards in pharmacogenetics: data model development and Delphi study

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Abstract

Background: Pharmacogenetics, a subset of precision medicine, leverages genetic testing to improve the safety and efficacy of prescribed medicines. Despite compelling evidence supporting its clinical and economic impact, widespread implementation remains limited. An established barrier to implementation is the lack of interoperable health information technology solutions that integrate pharmacogenetic data into frontline clinical workflows, particularly for non-specialist clinicians. Open data standards, such as openEHR and Fast Healthcare Interoperability Resources (FHIR) could address this by creating standardised, vendor-neutral formats for pharmacogenetic test results and thus enable precision medicine at scale.

Objective: This study aimed to develop and validate open data standards to represent pharmacogenetic data using openEHR and map these standards to HL7 FHIR to enable interoperability within healthcare systems.

Methods: We developed a baseline openEHR data model by synthesizing existing literature, genomic sequencing technology outputs, and international FHIR specifications. Using openEHR's Archetype Designer, an iterative design process was followed, informed by workshops with the Global Alliance for Genomics and Health (GA4GH). The model subsequently underwent two rounds of Delphi peer review involving 24 international experts across 10 countries providing a total of 30 reviews across both rounds. Mapping to HL7 FHIR was performed using both manual and automated approaches, including the FHIR-Connect tool.

Results: A standardised pharmacogenetic data model was developed, delineating "test results" from therapeutic implications to streamline clinical decision support (CDS). The final model incorporated globally recognized terminologies (e.g., SNOMED CT, HGNC) and was endorsed by the international expert Delphi review group. Published on the openEHR Clinical Knowledge Manager platform, the model achieved consensus for real-world deployment. HL7 FHIR mapping demonstrated successful bidirectional compatibility, supporting potential integration with English National Health Service (NHS) systems. Both manual and automated mapping approaches proved feasible, with the latter enabling scalable and reusable data transformations.

Conclusions: The study established a robust framework for storing and exchanging pharmacogenetic test results, addressing key barriers to precision medicine implementation. By separating test results from therapeutic implications and leveraging openEHR and FHIR, the proposed standards ensure semantic harmonisation and interoperability. These findings lay the groundwork for scalable implementation of pharmacogenetics, supporting CDS integration into routine care. Future efforts should focus on refining genomic data models, enhancing policy frameworks, and promoting cross-disciplinary collaboration to advance precision medicine. Clinical Trial: Not applicable

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Structured Abstract

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Keywords

Interoperability; medical informatics; clinical decision support systems; data standards; openEHR; FHIR

1. Introduction

Genetic testing can be used to improve the safety and effectiveness of commonly prescribed medicines. This is a concept known as ‘pharmacogenetics’ and comes under the umbrella of precision or personalised medicine. (1) Despite compelling scientific evidence on the potential clinical and economic impact of pharmacogenetics, implementation has been limited. (2) An important barrier to be overcome is the development of information technology solutions that support the integration of pharmacogenetics into healthcare systems and support every day prescribing decisions. (3)

Pharmacogenetics differs from traditional genomics as its application is not in specialist healthcare settings, but rather in settings where prescribing routinely occurs, such as general practice. As a result, there is a need to seamlessly share complex genomic data with clinicians who may have limited experience of using such information. (4) Therefore, pharmacogenetic data requires translation into a clinically relevant format (‘test results’) that can be understood by a new group of end-users. Such ‘test results’ need to be messaged from genomic laboratories to clinical systems, such as Electronic Health Record systems (EHRs), so they are available at the point of prescribing. (5) As prescribing is universal and occurs across the spectrum of healthcare services, a point-to-point messaging approach is not feasible as the number of integrations will be unmanageable; a more innovative strategy, that is ‘interoperable by design’ is therefore required. (6)

Across healthcare systems, interoperability is consistently identified as a key enabler of improved care coordination, patient experience and clinical outcomes. (7, 8) However, despite this clear need, interoperability remains an intractable challenge with healthcare systems globally continuing to struggle to meaningfully exchange data across geographies, providers and services. (9) Novel strategies, such as moving towards open standards-based platforms and prioritising interoperability at the outset of new technology initiatives can help shift this trend. (10)

The basis for effective interoperability in healthcare comes from aligning and standardising the meaning of clinical concepts; this is sometimes referred to as semantic harmonisation. (11) Different approaches to semantic harmonisation and development of open data standards exist. openEHR is now widely recognised as an approach which is supported by free, easy-to-use tooling and a wide international community of data modellers and editors to develop open data models for the storage of structured healthcare data. Fast Healthcare Interoperability Resources (FHIR) is being adopted by health systems as the primary approach to create standard data messages to communicate healthcare data between systems. Combining these approaches can lead to the development of open standards that can support an interoperable strategy.

Central to such a strategy is the need to store pharmacogenetic test results in a vendor-neutral and standardised format creating a single ‘source of truth’ for downstream use, such as through clinical decision support (CDS) systems or Health Information Exchange (HIE) solutions. However, there are currently no widely adopted open data standards for the storage of pharmacogenetic test results and this remains one of the key reasons why clinical implementation has been limited. (12) This project aims to address this by developing open data standards using openEHR and FHIR as well as using SNOMED-CT and other genomics ontologies to allow storage of standardised pharmacogenetic test results, and ultimately enable precision medicine across frontline care.

2. Methods

2.1 Context

This project was supported by the University of Manchester, the National Health Service (NHS)

England Network of Excellence in Pharmacogenetics and the Global Alliance for Genomics and Health (GA4GH). The project was delivered by a multidisciplinary team across genomics, clinical medicine and health informatics.

This project formed part of a wider research initiative titled “Pharmacogenetics Roll Out: Gauging Response to Service” (PROGRESS, ISRCTN15390784), which is a pilot programme aiming to implement pharmacogenetic testing in primary care across the NHS. The standards development work formed part of the informatics strategy of this programme, which also included user research, service design and development of CDS systems.

Due to the maturity of tooling and the accessible community, we used openEHR as the starting point in this project. OpenEHR is an open standard for modelling, storing, and retrieving health data. (13) Development of openEHR data models (known as archetypes) are dependent on a unified effort between technologists and clinicians. (14) The Clinical Knowledge Manager (CKM) tool (Ocean Health Systems ©) provides a free collaborative platform for the iterative design of archetypes and for an asynchronous Delphi peer review process. The CKM subsequently acts as a library of published archetypes that have been peer reviewed and deemed suitable for real-world deployment. This provides an open community-based governance process for the management of archetypes.

2.2 Data model development and consensus agreement

We developed a baseline model based on existing research and worked with an international community of scientific, clinical and informatics experts to refine the model and agree consensus. The baseline model included concept headings, data elements, together with their descriptions and a proposed hierarchy between elements. An expert editorial board consisting of experts in

pharmacogenetics (authors JM, JK and WN) and clinical informatics (authors VS and IM) was formed. The editorial board was further supported by experienced openEHR data modellers, including broader genomics modelling experts, from the international community to apply formal governance.

We reviewed the current genomic sequencing technology outputs in the form of CSV and JSON files to identify the key data elements reported. We mapped those in a mind map and compared these with a previous FHIR pharmacogenetic reporting specification (2022). (15) We presented this mind map together with background on pharmacogenetics at a series of discovery workshops through a new pharmacogenetics data standardisation working group within GA4GH. These workshops informed the design of a baseline data model using the free *Archetype Designer* tool (openEHR international / Better ®).

The data model subsequently underwent two rounds of review using a Delphi peer review process. Reviewers included members of the international openEHR and GA4GH community (14 and 16 reviewers per round respectively). Feedback and comments were discussed over the course of three editorial meetings and revisions were made to finalise the data model for publication. Figure 1 summarises the data model development process.

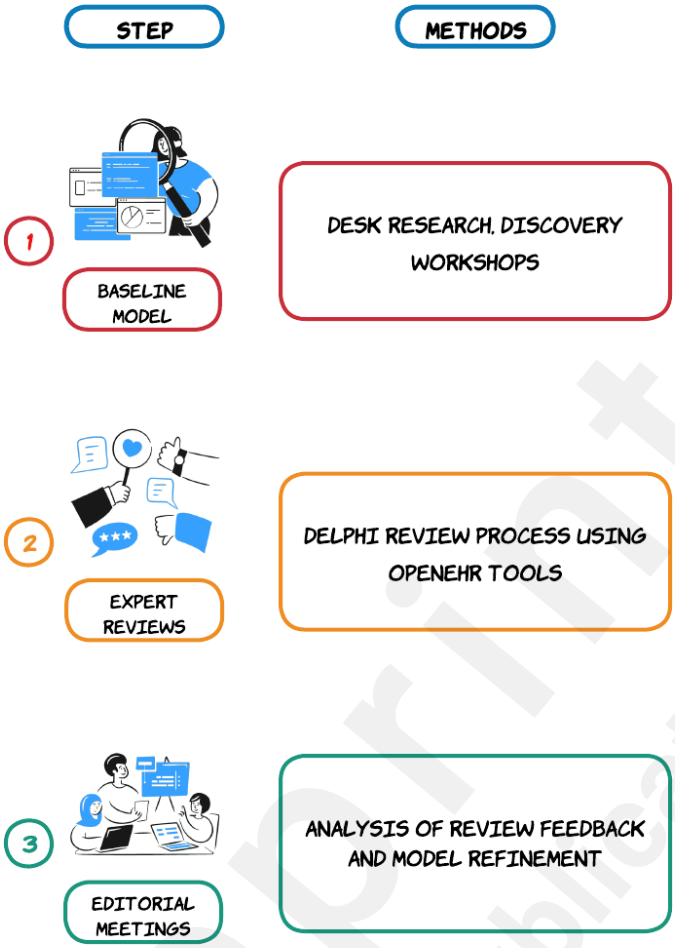

Figure 1: diagrammatic overview of the data model development, Delphi peer review process and model refinement for publication

2.3 HL7 FHIR mapping

An additional key requirement of this project was to demonstrate that an openEHR based data model could communicate with the wider NHS England healthcare community via HL7 FHIR-based messages and Application Programming Interfaces (APIs). NHS England is developing a set of test requesting data standards based on the FHIR Genomics Reporting Implementation Guide. (15)

Therefore, a set of mappings between the openEHR data model and the FHIR implementation guide were developed and were applied using two different approaches:

1. a manual approach requiring Java software development
2. an automated approach using the *FHIR-Connect* tool (Better®) (https://github.com/better-care/fhir-connect-mapping-spec/)

3. Results

3.1 Baseline data model

We identified that previous research and FHIR specifications had combined the pharmacogenetic test result data elements i.e. information related to the patients' genetic results, and thus their predicted ability to metabolise medicines, with data elements related to the therapeutic implications for individual medicines. We hypothesised that these are distinct concepts, which should be modelled separately, and this was echoed by experts in the GA4GH working group. A 'pharmacogenetic test result' data model should only capture information directly related to the individual, which is permanent, and the therapeutic implications for medicines should be inferred based on the test result data as part of CDS systems and knowledgebases, which can change over time.

3.2 Final data model

The Delphi process involved peer reviewers across 10 different countries and included a range of healthcare, laboratory and information technology professionals. Table 1 summarises the geographic and professional spread of reviewers

Table 1: geographic and professional spread of reviewers involved in the Delphi process (N=number of reviewers)

Geography	**N**	**Profession**	**N**
Australia	3	Pharmacist	2
Finland	1	Doctor	5

India	2	Nurse	2
Italy	3	Health IT	13
New Zealand	1	Laboratory	2
Norway	4		
Spain	1		
Sweden	1		
United Kingdom	5		
United States	3		

Through an iterative process we finalised the names of the data elements, their descriptions and intended uses. The data elements that could be bound to existing terminologies, such as HUGO Gene Nomenclature Committee (HGNC) were included, as well as the standardised consensus LOINC and SNOMED CT terms recommended by the Clinical Pharmacogenetics Implementation Consortium (CPIC). (16) Full details of all the data elements can be found in supplement I and viewed on the CKM website. (https://ckm.openehr.org/ckm/archetypes/1013.1.7066). The approved archetype (v1.0) was published on 22/11/2024 and is visualised as a mind map in Figure 2.

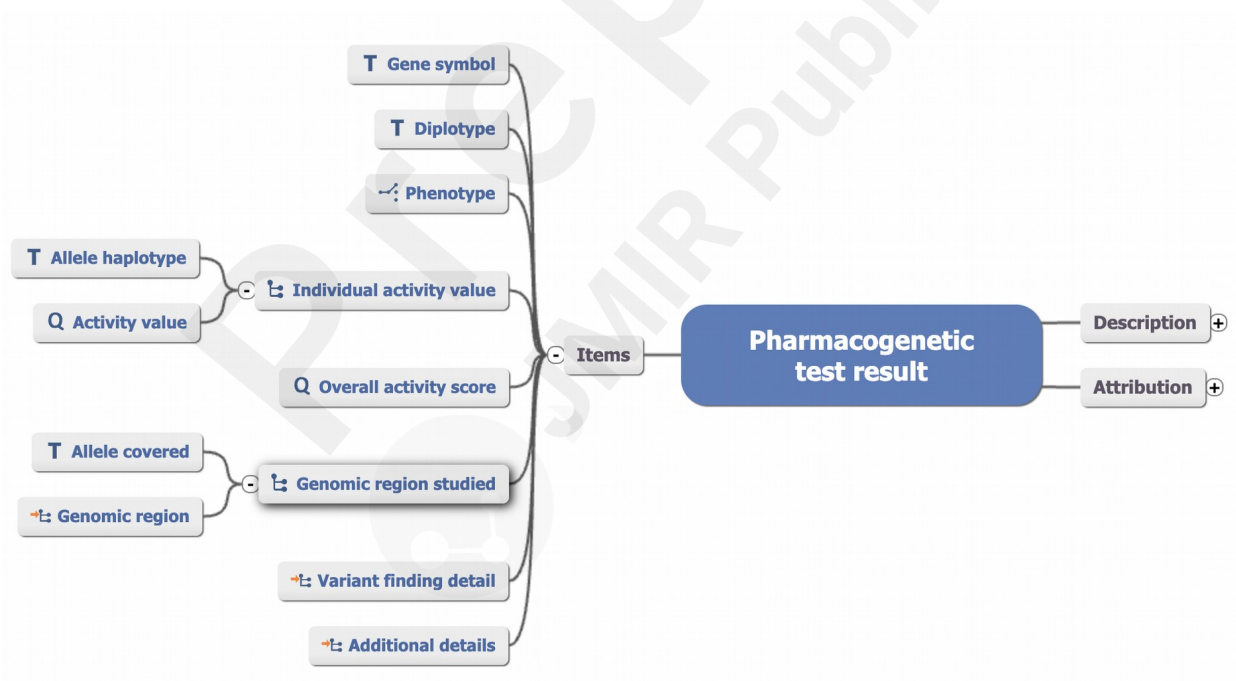

Figure 2: mind map of the final openEHR data model (archetype), summarising data elements

3.3 Results from HL7 FHIR mapping

Results of the two approaches to FHIR mapping are described:

1) Manual approach: Mappings were created using a table linking openEHR data fields to equivalent FHIR fields. Custom software could then convert data between the two formats. This method worked well but required some manual effort.

2) FHIR Connect: This open specification allowed bi-directional declarative mappings to be created between openEHR and FHIR. A custom transform engine, based on that specification, reads the source data and creates the target output automatically. This approach allows FHIR Connect mappings to be shared across different openEHR implementations and an open-source version of the transform engine is being developed.

Mappings were successfully identified for all the datapoints in the openEHR archetype to an equivalent node in a FHIR Bundle based on the FHIR Genomics Diagnostic Report, including appropriate use of SNOMED CT terms to carry CPIC phenotype coded values, such as metaboliser states. Example mappings annotated as openEHR and FHIR data fields were then then used to construct FHIR-Connect definitions. An example FHIR connect mapping is provided in the supplementary material (supplement II).

4. Discussion

This paper reports on development of an open data model to store pharmacogenetic test results using openEHR and explored the subsequent requirements for mapping these to HL7 FHIR. This adds novel data to the current body of literature on the role of interoperability and standards to support more widespread use of precision medicine in frontline care.

4.1 Implications for clinical practice

The traditional output from genetic testing, such as in the context of rare disease or cancer is a ‘genetic report’. This is usually generated as a paper output or PDF file which cannot be interrogated. The broader literature on pharmacogenetics similarly refers to ‘reports’ as the modality to share outputs of testing with healthcare professionals and patients. (17) This paper argues that for pharmacogenetics to be implemented at scale and integrated into frontline practice, such as primary care, a shift is needed. Specifically, there is a need to move from producing detailed 'reports' intended for specialists, to generating concise 'test results' relevant to prescribing decisions and designed for generalists, akin to other routine diagnostics, such as how a renal function result might be used to guide the dosing of a medicine. The use of genetic variation in healthcare holds significant potential. However, for successful adoption, innovation will need to follow a process that simplifies complexity and meaningfully considers the end-users. (18)

In the context of pharmacogenetics, there is significant value of test results within the prescribing workflow in the form of CDS systems. (19) Similar to other predictive insights, this requires integration with EHRs to generate meaningful use. (20) The reported implementations of pharmacogenetic CDS systems have focussed on individual centres, primarily in the USA, working with their local EHR provider to integrate pharmacogenetics, such as at the Mayo Clinic. (21) The eMERGE-PGx project (also USA) aimed to undertake a collective PGx implementation across 10 participating sites, which included EHR integration and CDS - this project has contributed to some of the reports on the use of FHIR to drive standardisation, however a publication on whether the intended benefits were achieved is awaited. (22, 23)

One of the relevant outputs from the eMERGE-PGx work was the concept of ‘genomic indicators’, which essentially provide a ‘home’ for genomic results, such as pharmacogenetics, within an EHR. (24) This reflects the requirement that genetic test results differ in their nature to existing health informatics concepts, such as ‘observation’ or ‘diagnosis’; trying to fit genetics into a construct that does not reflect its clinical impact, intended use or longitudinal relevance may not be appropriate. In addition, individual pharmacogenetic test results may cover a single gene or multiple genes and for each gene include a range of variants; it is therefore likely that an individual may have multiple pharmacogenetic tests across their lifetime, and clinical decision making at any given time must be based on the cumulative derivation of these multiple test results at that point. This further makes the case for a separate concept, such as ‘pharmacogenetic profile’ or indeed ‘genomic indicator’, which acts as the single ‘source of truth’. Further work is required to mature these ideas and develop the standards that can support the next layer of innovation in this field. Figure 3 visualises the genomic indicator concept.

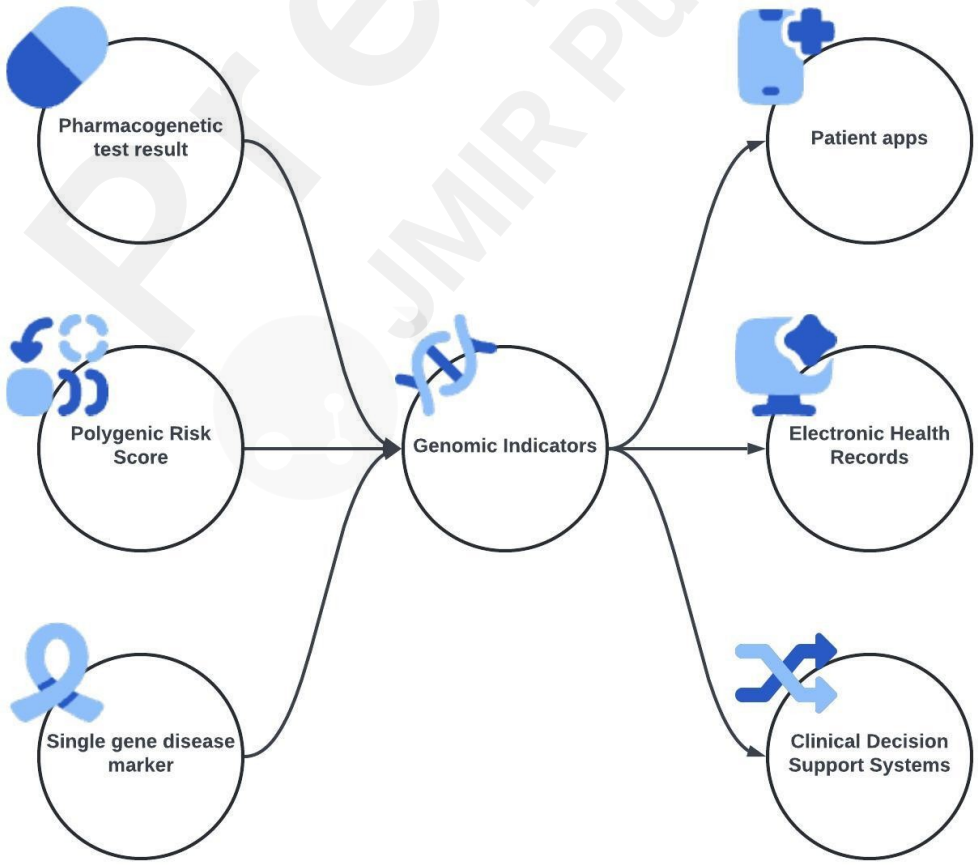

Figure 3: a genomic indicator concept could provide a data model to shift the concept of 'test reports' to actionable 'test results for genomic data that is more widely used across a health system, such as pharmacogenetic test results, polygenic risk scores (e.g. cardiovascular) and single gene disease markers (e.g. inherited breast cancer risk).

4.2 Implications for policy

In the field of health data standards there is continued debate between which standard is most appropriate. For pharmacogenetics, explicit semantic harmonisation was recognised as a critical component for the use of results in EHRs. (25) openEHR offers the most natural collaborative Delphi methodology and tooling to reach focussed international multi-stakeholder consensus and therefore was a natural place to start. (26) In addition, openEHR promotes a 'maximum dataset' philosophy, which means we could gather broad clinical concepts and represent them in the standard. Subsequent mapping to other standards, eg. FHIR, which takes an 80/20 dataset philosophy is therefore readily feasible, whereas if we started with FHIR, mapping to openEHR (or other standards, such as OMOP) would not have been possible. (27) This approach is increasingly being recognised by clinical and digital leaders, with several national policies including the need for converging on openEHR and FHIR to shift the dial on interoperability. (28, 29)

The successful integration of pharmacogenetics into routine frontline care requires more than technological solutions; it demands a coordinated policy covering clinical guidelines, healthcare professional education and patient and public engagement. Whilst policymakers should prioritise the adoption of open data standards, collaboration with professional associations, such as the Royal College of General Practice (UK) or the American Medical Association can promote precision medicine amongst wider communities outside of genetics. Finally, there remains a need to consider regulatory frameworks that safeguard the role of CDS systems as they impact clinical care and decision-making to ensure they are assessed for safety and variation.

5. Conclusion

The integration of pharmacogenetics into routine care has the potential to significantly improve patient care and outcomes. However, the lack of open data standards remains a key barrier to widespread implementation. Using openEHR and FHIR, we developed an open data model to represent a pharmacogenetic test result. This will enable the standardised and structured storage of data and act as the ‘single source of truth’ to support clinical implementation and CDS systems. This interoperable approach can ensure pharmacogenetic test results are made available across healthcare settings and enable precision medicine at scale.

6. Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

Not applicable.

Declarations of interests

V.S, W.N. and J.M are co-founders of an early-stage health technology start-up, Fava Health Ltd.

IM is a director at freshEHR Clinical Informatics©.

HK is an employee at freshEHR Clinical Informatics©.

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Authors' contributions

VS conceptualised the study; VS, IM led on the clinical modelling exercise; VS and JM led the GA4GH pharmacogenetics working group; IM organised and prepared the Delphi Reviews; VS, IM, JM, and JK reviewed the results and developed the final data model; VS wrote the manuscript; all authors reviewed and approved the manuscript for publication.

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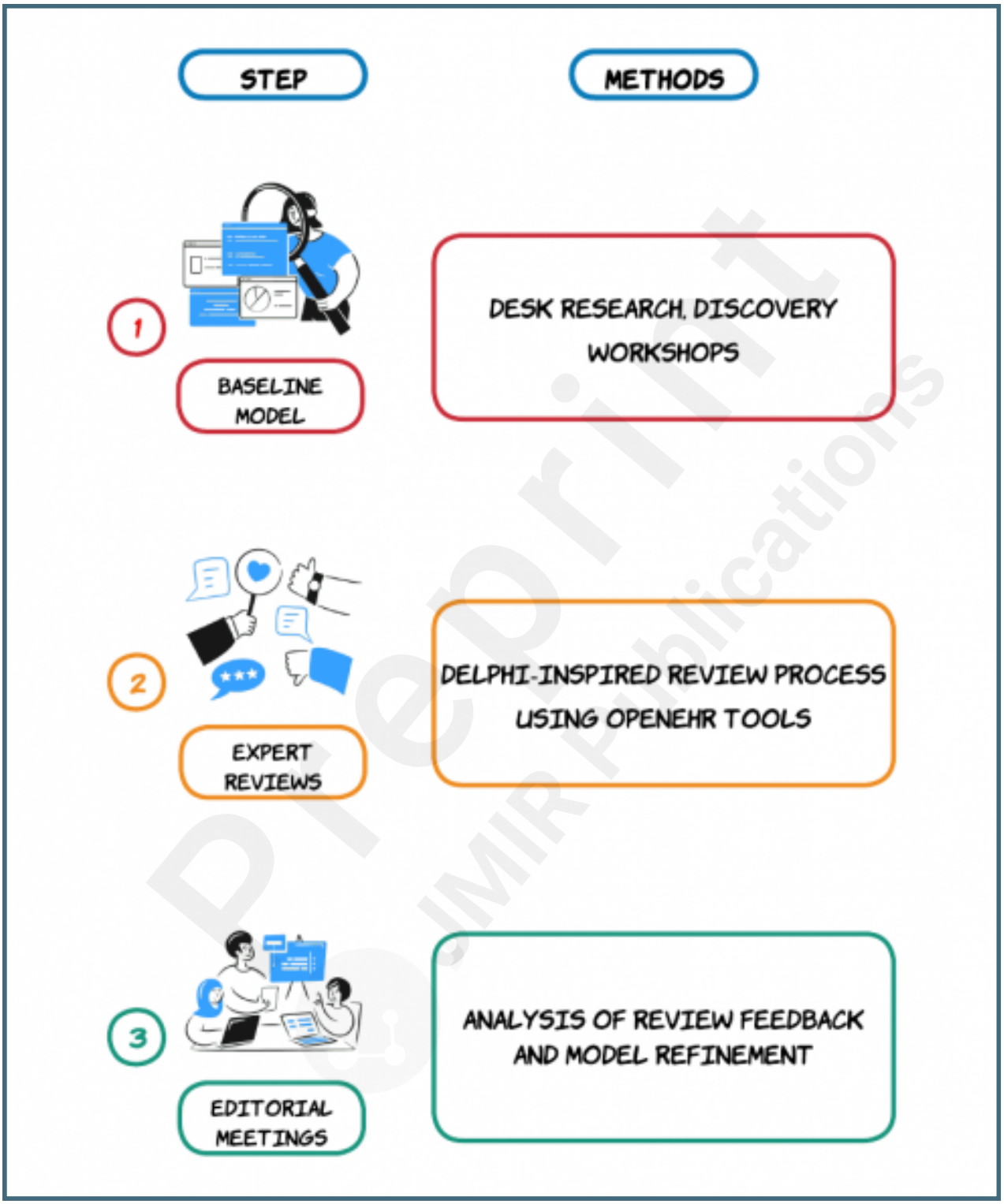
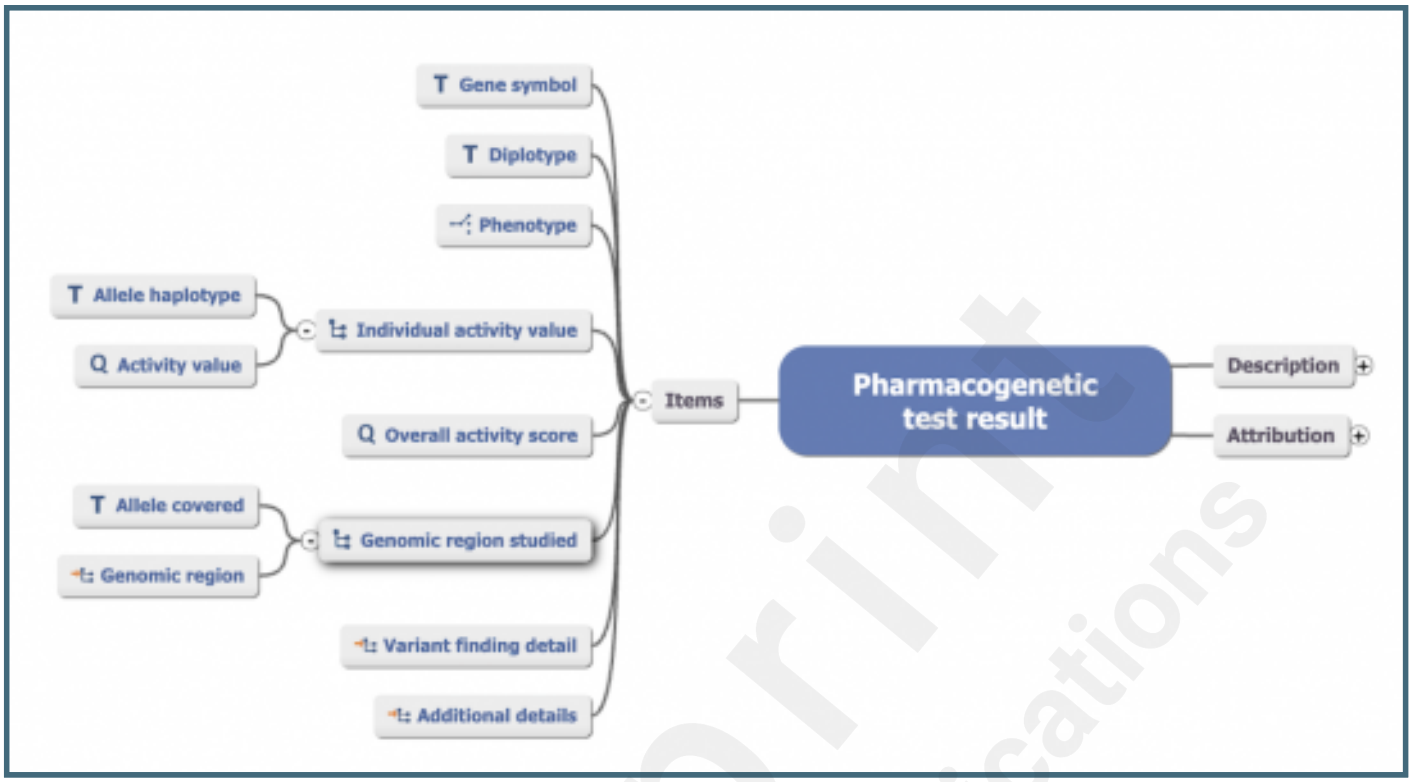
Supplementary Files

Figures

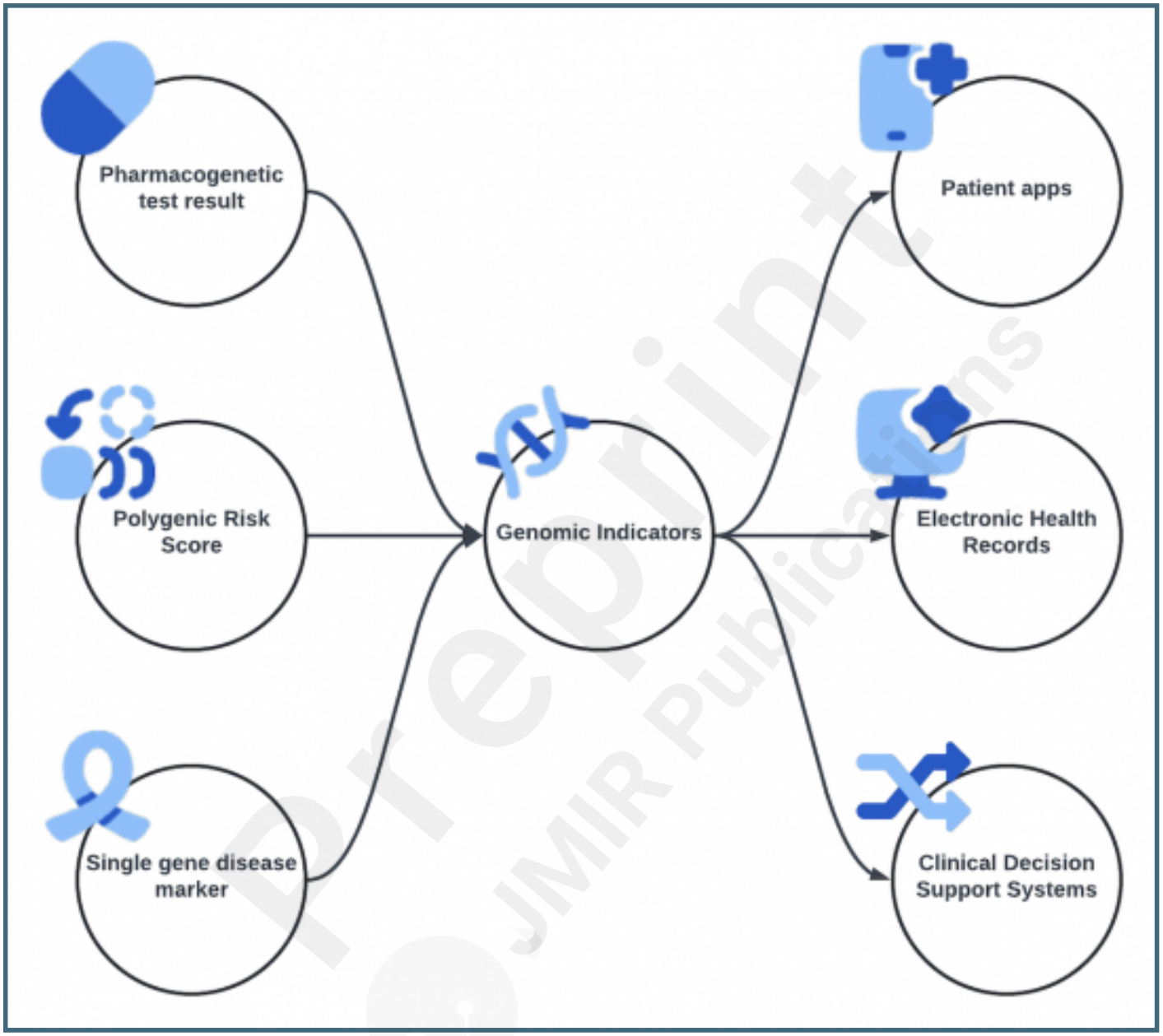
Diagrammatic overview of the data model development, Delphi peer review process and model refinement for publication.



Mind map of the final openEHR data model (archetype), summarising data elements.



A genomic indicator concept could provide a data model to shift the concept of ‘test reports’ to actionable ‘test results for genomic data that is more widely used across a health system, such as pharmacogenetic test results, polygenic risk scores (e.g. cardiovascular) and single gene disease markers (e.g. inherited breast cancer risk).



Multimedia Appendixes

Details of the elements in the final data model.
URL: http://asset.jmir.pub/assets/760bd44abfd7dbbf8aeede2fdd7102a4.pdf

Example mappings between openEHR and FHIR data elements.
URL: http://asset.jmir.pub/assets/b89971434e9ff3a18ac539fc50d21a01.xlsx