The GA4GH Phenopacket schema: A computable representation of clinical data for precision medicine

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To the editor. Despite great strides in the development and wide acceptance of standards for exchanging structured information about genomic variants, the development of standards for computational phenotype analysis for translational genomics has lagged behind. Phenotypic features (signs, symptoms, laboratory and imaging findings, results of physiological tests, etc.) are of essential clinical importance, yet exchanging them in conjunction with genomic variation is often overlooked or even neglected. In the clinical domain, significant work has been dedicated to the development of computational phenotypes.[1] Traditionally, these approaches have largely relied on rule-based methods and large sources of clinical data to identify cohorts of patients with or without a specific disease.[2–5] However, they were not developed to enable deep phenotyping of phenotypic abnormalities, to facilitate computational analysis of interpatient phenotypic similarity, or to support computational decision support. To address this, the Global Alliance for Genomics and Health[6] (GA4GH) has developed the Phenopacket schema, which supports exchange of computable longitudinal case-level phenotypic information for diagnosis of and research on all types of disease including Mendelian and complex genetic diseases, cancer, and infectious diseases (Fig 1).

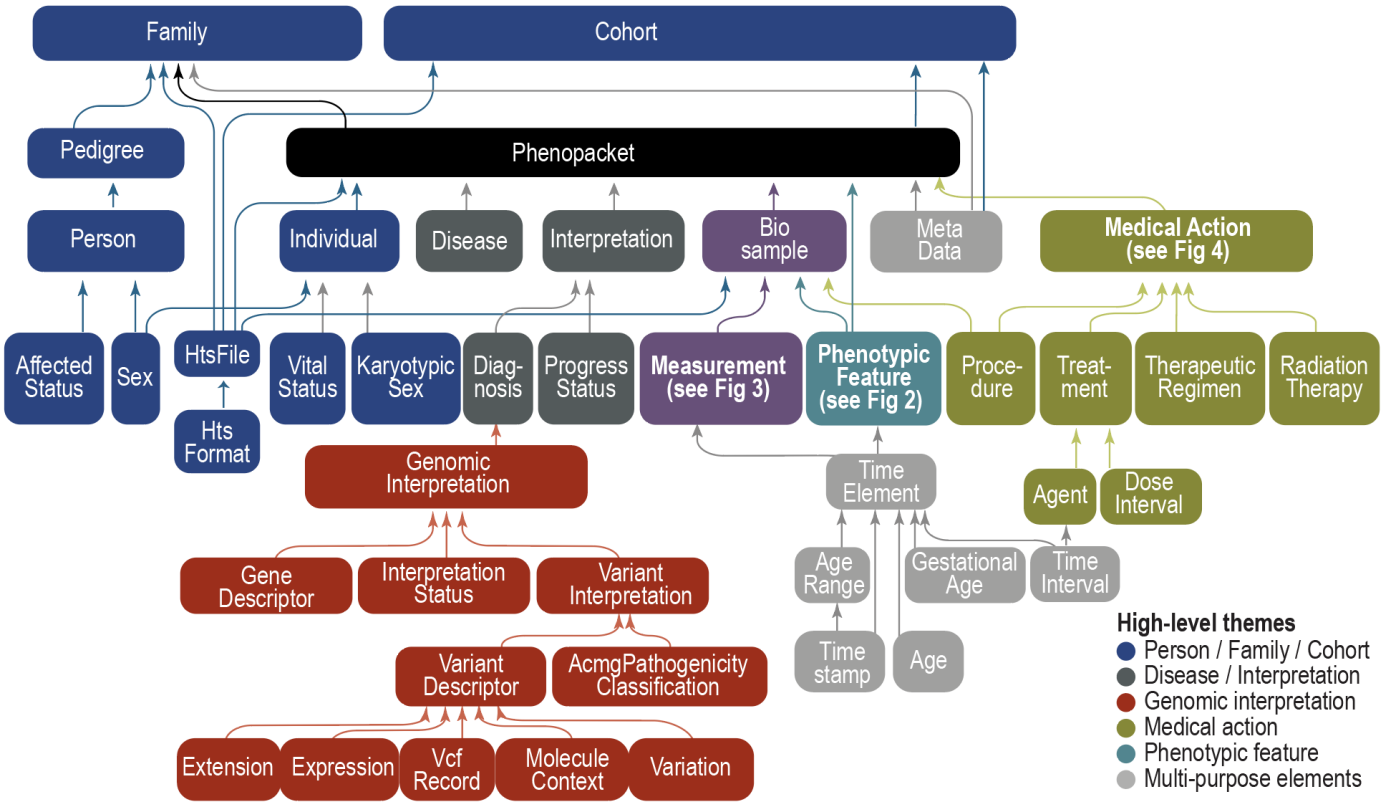

Figure 1. Phenopacket schema overview. *The GA4GH Phenopacket schema consists of several optional elements, each of which contains information about a certain topic such as phenotype, variant, pedigree, etc. An element can contain other elements, which allows a hierarchical representation of data. For instance,* `Phenopacket` *contains elements of type* `Individual`, `PhenotypicFeature`, `Biosample`, *and so on. Individual elements can therefore be regarded as building blocks that are combined to create larger structures. Colors represent the major themes of elements within the schema.*

The *PhenotypicFeature* is the central element of the Phenopacket schema. A *PhenotypicFeature* can be used to describe any phenotypic characteristic (often, but not necessarily, clinical abnormalities) including signs and symptoms, laboratory findings, histopathology findings, imaging, electrophysiological results, etc., along with modifier and qualifier concepts. Each phenotypic feature is described using an ontology term. While the Phenopacket schema does not mandate which ontology to use, it provides recommendations, such as the Human Phenotype Ontology[7] (HPO) for rare diseases and the National Cancer Institute Thesaurus (NCIT) for transmission of information about a cancer specimen, e.g., pathological staging or more detailed information about histology or tumor markers.[8] One can indicate whether an abnormality was excluded during the diagnostic process (e.g., whether a morphological cardiac defect was excluded by echocardiography), or use other optional HPO terms to denote the severity, frequency (e.g., number of occurrences of seizures per week), laterality (e.g., unilateral), or other pattern of a phenotypic feature in the patient being described. Finally, the onset (and if applicable the resolution) of specific features can be indicated. Other key elements are *Measurement*, which is used to capture quantitative (i.e., numerical), ordinal (e.g., absent/present), or categorical measurements; *Biosample*, a description of biological material obtained from the individual represented in the Phenopacket and used for phenotypic, genotypic, or other -omics analysis; and *MedicalAction*, which includes a hierarchical representation of medical actions including medications, procedures, and other actions taken for clinical management. The *Treatment* element is a subelement of *MedicalAction* and represents administration of a pharmaceutical agent, broadly defined as prescription and over-the-counter medicines, vaccines, and other therapeutic agents such as monoclonal antibodies or CAR T-cell-therapy.

The *Interpretation* elements specify interpretations of genomic findings. This element leverages complementary resources developed by the GA4GH Genomic Knowledge Standards Work Stream: the Variation Representation Specification (VRS) and VRS Added Tools for Interoperable Loquacious Exchange (VRSATILE; see Web Resources).[6] Further information on this and other elements is available in the online documentation.

The Phenopacket schema was designed to support a number of use cases. Many of these use cases have been successfully implemented and tested in the community, particularly in the field of rare disease diagnostics and biobanking, while others, such as EHR integration, are in the process of being implemented (Supplemental Table 1).

The Phenopacket schema (version 2.0) was formally reviewed and approved as a GA4GH standard[6] in 2021. It is designed to be interoperable with other relevant standards, including the traditional PED file as well as the GA4GH pedigree standard, the GA4GH Beacon,[9] and the GA4GH Variation Representation Specification. The GA4GH has committed to coordinate its activities and future roadmaps with those of other standards development organizations (SDOs), including International Organization for Standardization (ISO) Technical Subcommittee for Genomics Informatics (ISO/TC215/SC1) and HL7 Clinical Genomics (CG). Consequently, a Fast Interoperable Healthcare Resources (FHIR) implementation guide for Phenopacket interoperability is being developed and the Phenopacket schema is in the process of ISO certification (Supplemental Table 2).

The VCF standard for storing genotyping data allowed a wide range of research groups to write software for analyzing such data.[10] The GA4GH Phenopacket schema aspires to be similarly transformative in the landscape of genome analysis using phenotype data. Multiple providers of phenotypic data include patients and clinicians, via a variety of mechanisms including clinical notes and EHR records, interfaces such as FHIR, app-based entry, and mobile devices. The Phenopacket schema acts as a common model that can capture data from many sources with a unified software representation and in turn can be used by multiple receivers of the phenotypic information, including journals, databases, registries, clinical laboratories. Phenopackets can support diverse users and use cases, including patient matchmaking services, diagnostics, and cohort identification. Software has become an essential resource for genomic medicine. We anticipate that the Phenopacket schema will encourage the development of a collection of software for the analysis of genomic data in the context of clinical information that will accelerate innovation and discovery. Genomic data will become ever more important in translational research and clinical care in the coming years and decades. The Phenopacket schema represents a standard for capturing clinical data and integrating it with genomic data that will help to obtain the maximal utility of this data for understanding disease and developing precision medicine approaches to therapy.

Core Phenopacket resources - Software availability:

Phenopacket schema source code: https://github.com/phenopackets/phenopacket-schema

Phenopacket schema documentation: https://phenopacket-schema.readthedocs.io/

Phenopacket tools: https://github.com/phenopackets/phenopacket-tools

Related Standards - Web Resources:

GA4GH Beacon project: https://beacon-project.io/

GA4GH Phenopacket FHIR implementation guide: https://github.com/phenopackets/core-ig

GA4GH Pedigree standard: https://github.com/GA4GH-Pedigree-Standard/pedigree

GA4GH Variation Representation Specification (VRS): vrs.ga4gh.org

VRS Added Tools for Interoperable Loquacious Exchange (VRSATILE): vrsatile.readthedocs.io

Phenopacket RDF model: https://github.com/LUMC-BioSemantics/phenopackets-rdf-schema/wiki

Genomics Informatics — Phenopackets: A Format for Phenotypic Data Exchange (ISO): https://www.iso.org/standard/79991.html

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Acknowledgements

The authors gratefully acknowledge insight and feedback from Marian H. Adly, Pier Luigi Buttigieg, Nour Gazzaz, Janine Lewis, Manuel Posada de la Paz and Maria Taboada.

Funding

This work was supported by 7RM1HG010860-02 (NHGRI). Additional funding was as follows. PNR was supported by NLM contract #75N97019P00280, NIH NHGRI RM1HG010860, NIH OD R24OD011883, NIH NICHD 1R01HD103805-01. HH was supported by NIH OD R24OD011883. GIS was supported by ELIXIR, the research infrastructure for life-science data. CGC was supported by NIH NCATS U24TR002306. KCL was supported by NIH OD 5UM1OD023221. MB was supported by BioMedIT Network project of Swiss Institute of Bioinformatics (SIB) and Swiss Personalized Health Network (SPHN). AHW was supported by NIH NHGRI K99HG010157, NIH NHGRI R00HG010157. CJM, MAH, MCM-T, JAM, DD were supported by NIH NHGRI RM1HG010860, NIH OD R24OD011883. AM-J was supported by Australian Genomics. Australian Genomics is supported by the National Health and Medical Research Council (GNT1113531). DS, JOBJ were supported by NIH NHGRI RM1HG010860, NIH OD R24OD011883, NIH NICHD 1R01HD103805-01. MD was supported by NIH NHGRI U54HG004028, NIH NHGRI 5U01HG008473-03, NIH NCATS OT2TR003434-01S1U54HG008033-01. GSB was supported by Roy Hill Community Foundation, Angela Wright Bennett Foundation, McCusker Charitable Foundation, Borlaug Foundation, Stan Perron Charitable Foundation. LB was supported by NIH NHGRI U41HG006834 (Clinical Genome Resource). MC was supported by EMBL-EBI Core Funds and Wellcome Trust GA4GH award number 201535/Z/16/Z. AH was supported by NIH NHGRI 1U41HG006627, NIH NHGRI 1U54HG006542, NIH NHGRI 1RM1HG010860. PNS was supported by The Alan Turing Trust. NLH was supported by NIH NHGRI RM1HG010860, NIH OD R24OD011883, U.S. Department of Energy Contract DE-AC02-05CH11231. NP was supported by Moorfields Eye Charity. NQ-R was supported by EU Horizon 2020 research and innovation programme grant agreement 825575 (EJP-RD). OE was supported by NIH grants UL1TR002384, R01CA194547, P01CA214274 LLS SCOR grants 180078-01, 7021-20, Starr Cancer Consortium Grant I11-0027. HL was supported by CIHR Foundation Grant on Precision Health for Neuromuscular Diseases FDN-167281. RT was supported by CIHR postdoctoral fellowship award MFE-171275. LDS was supported by Genome Canada and NIH NHGRI U24HG011025. SO was supported by AMED. DP, LM, AP, SB, MR, RK were supported by EU Horizon 2020 research and innovation programme grant agreements 779257 (Solve-RD) and 825575 (EJP-RD). RRF was supported by NLM contract #75N97019P00280.

Conflicts of interest

SK is an employee of Ada Health GmbH. NP is a director of Phenopolis Ltd. OE is supported by Janssen, Johnson and Johnson, Volastra Therapeutics, AstraZeneca and Eli Lilly research grants. He is scientific advisor and equity holder in Freenome, Owkin, Volastra Therapeutics and One Three Biotech. ARM is an employee of Philips Research North America. OJB is an employee of PhenoTips. MA is an editor employed by Wiley. AS is an employee of Lifebit Biotech Ltd.

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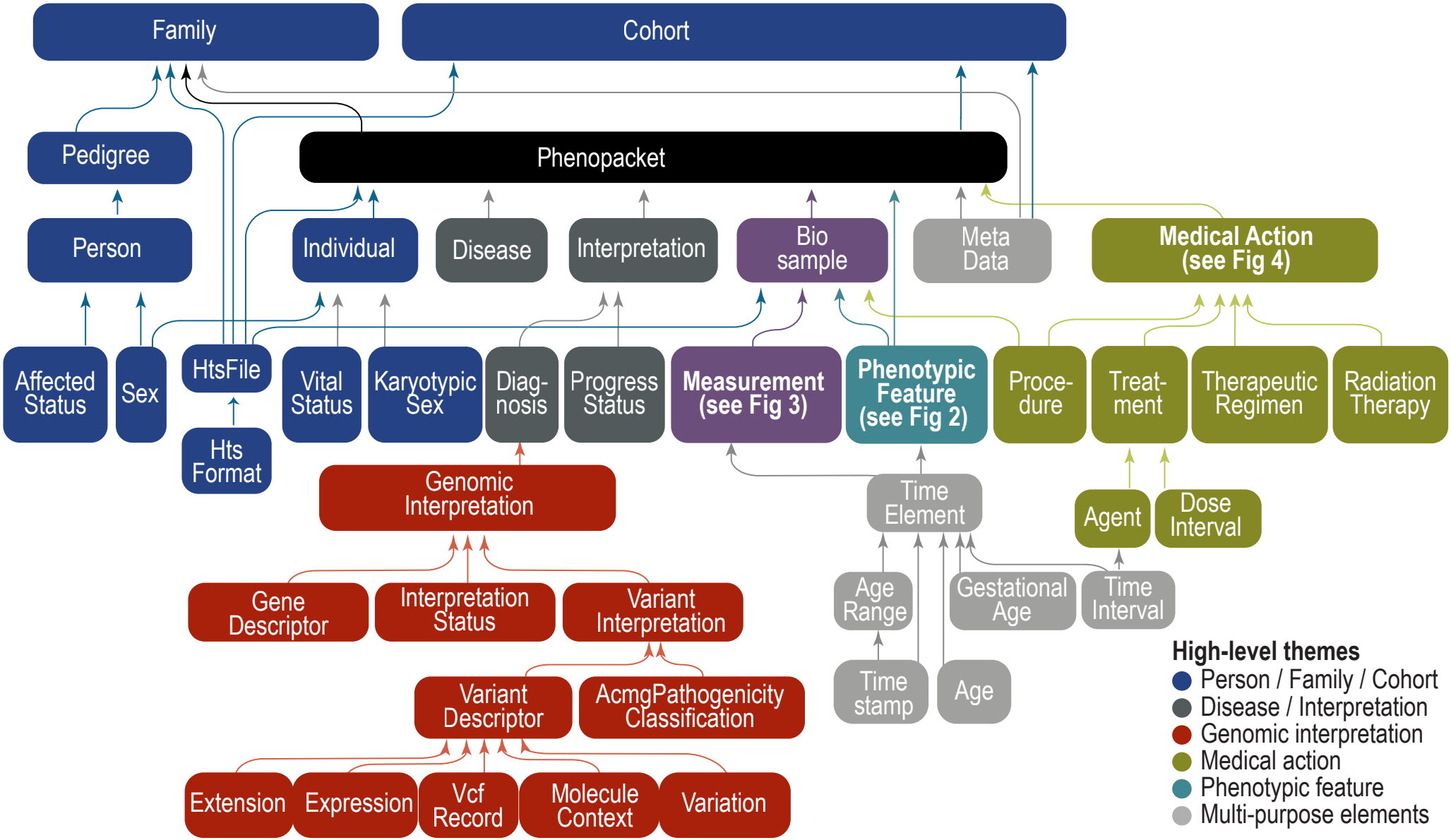
Family
Cohort
Pedigree
Phenopacket
Person
Individual
Disease
Interpretation
Bio sample
Meta Data
Medical Action (see Fig 4)
Affected Status
Sex
HtsFile
Vital Status
Karyotypic Sex
Diag-nosis
Progress Status
Measurement (see Fig 3)
Phenotypic Feature (see Fig 2)
Proce-dure
Treat-ment
Therapeutic Regimen
Radiation Therapy
Hts Format
Genomic Interpretation
Time Element
Agent
Dose Interval
Gene Descriptor
Interpretation Status
Variant Interpretation
Age Range
Gestational Age
Time Interval
Variant Descriptor
AcmgPathogenicity Classification
Time stamp
Age
Extension
Expression
Vcf Record
Molecule Context
Variation
High-level themes
Person / Family / Cohort
Disease / Interpretation
Genomic interpretation
Medical action
Phenotypic feature
Multi-purpose elements