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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, progress in 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 high clinical importance, yet exchanging them in conjunction with genomic variation is often overlooked or even neglected. In the clinical domain, substantial 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 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). The Phenopacket software is available at https://github.com/phenopackets/.

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, and electrophysiological results, along with modifier and qualifier concepts. Each phenotypic feature is described using an ontology term. Although 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] Within the schema, it is possible to indicate whether an abnormality was excluded during the diagnostic process (e.g., whether a morphological cardiac defect was excluded by echocardiography) or to 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 of the schema 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 chimeric antigen receptor (CAR)-T-cell-therapy.

The 'Interpretation' element specifies 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).[6] Further information on this and other elements is available in the online documentation (https://phenopacket-schema.readthedocs.io/).

The Phenopacket schema was designed to support several 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, whereas others, such as electronic health record integration, are in the process of being implemented (Supplementary 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 (pedigree format) 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, including the 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 (Supplementary Table 2).

The variant call format (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 electronic health 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, and 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.

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Competing interests

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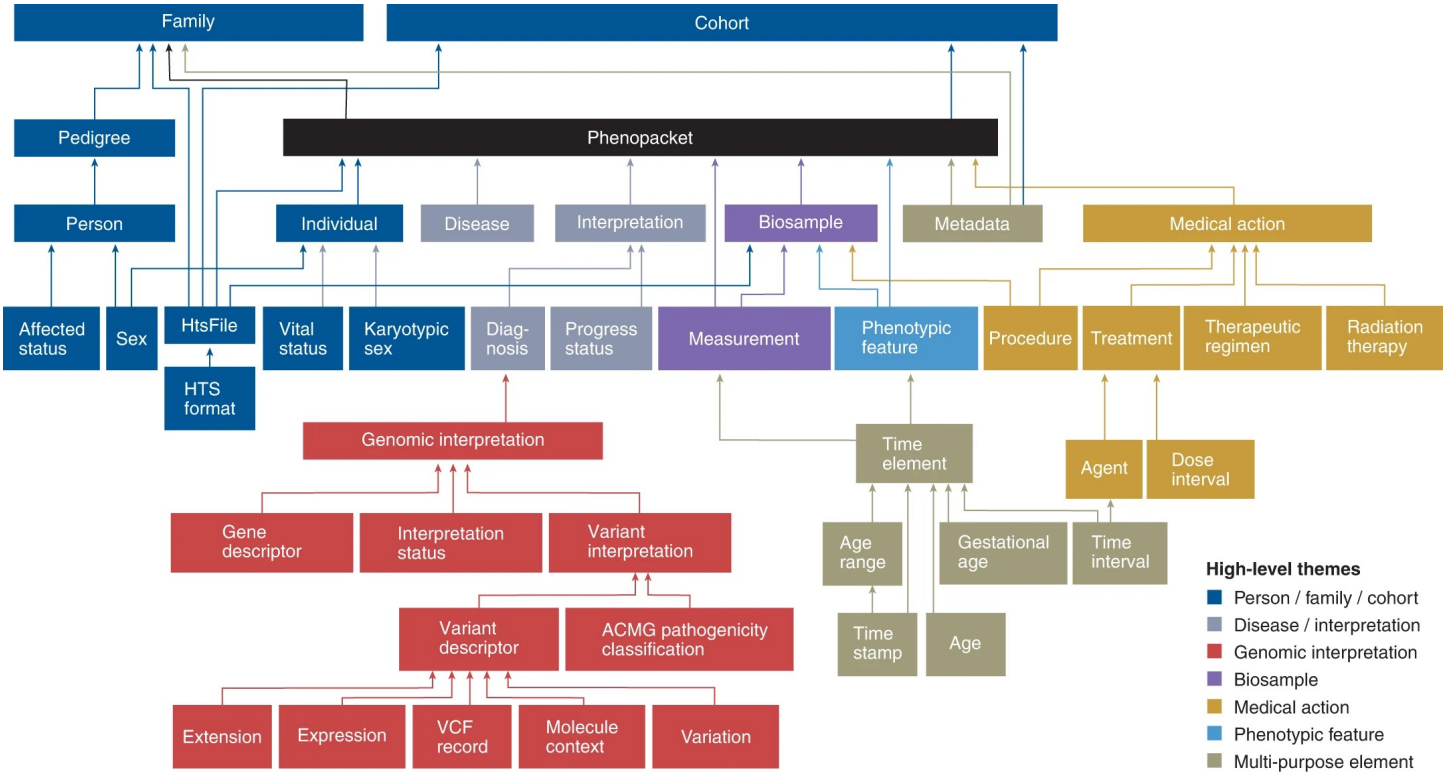

Figure 1. Phenopacket schema overview. The GA4GH Phenopacket schema consists of several optional elements, each of which contains information about a certain topic, such as phenotype, variant or pedigree. An element can contain other elements, which allows a hierarchical representation of data. For instance, 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.