Harmonizing and sharing phenotypes across organisms for diagnostics and mechanism discovery

The Monarch Initiative

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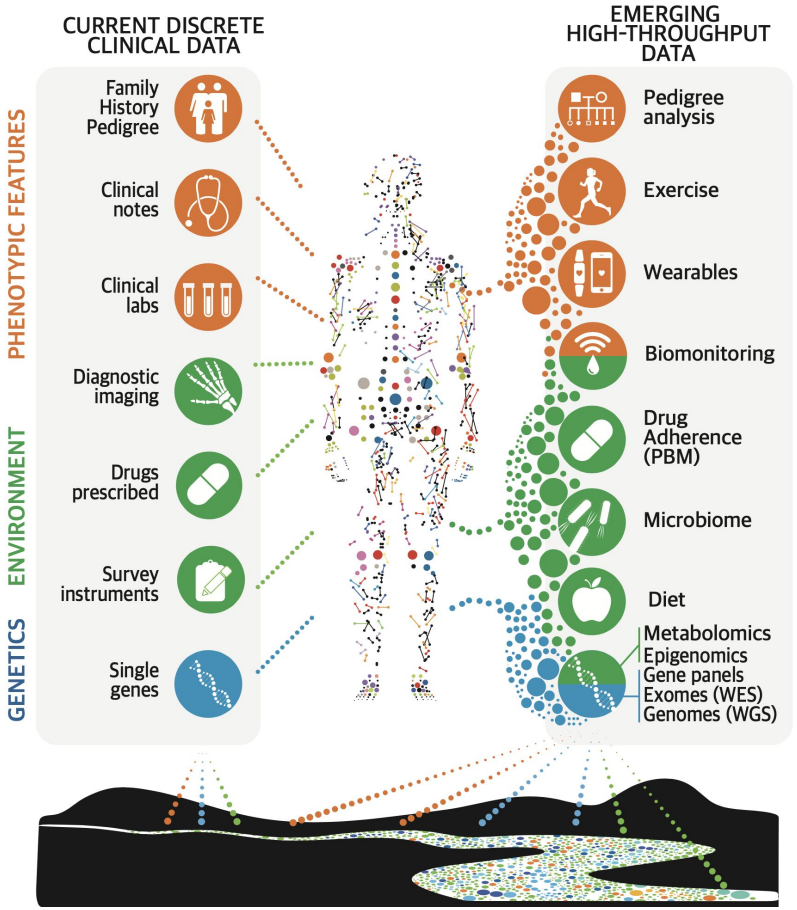
3 August, 2021

These slides bit.ly/mi-risk-s3



Clinical Phenotyping & Diagnostics

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monarchinitiative.org

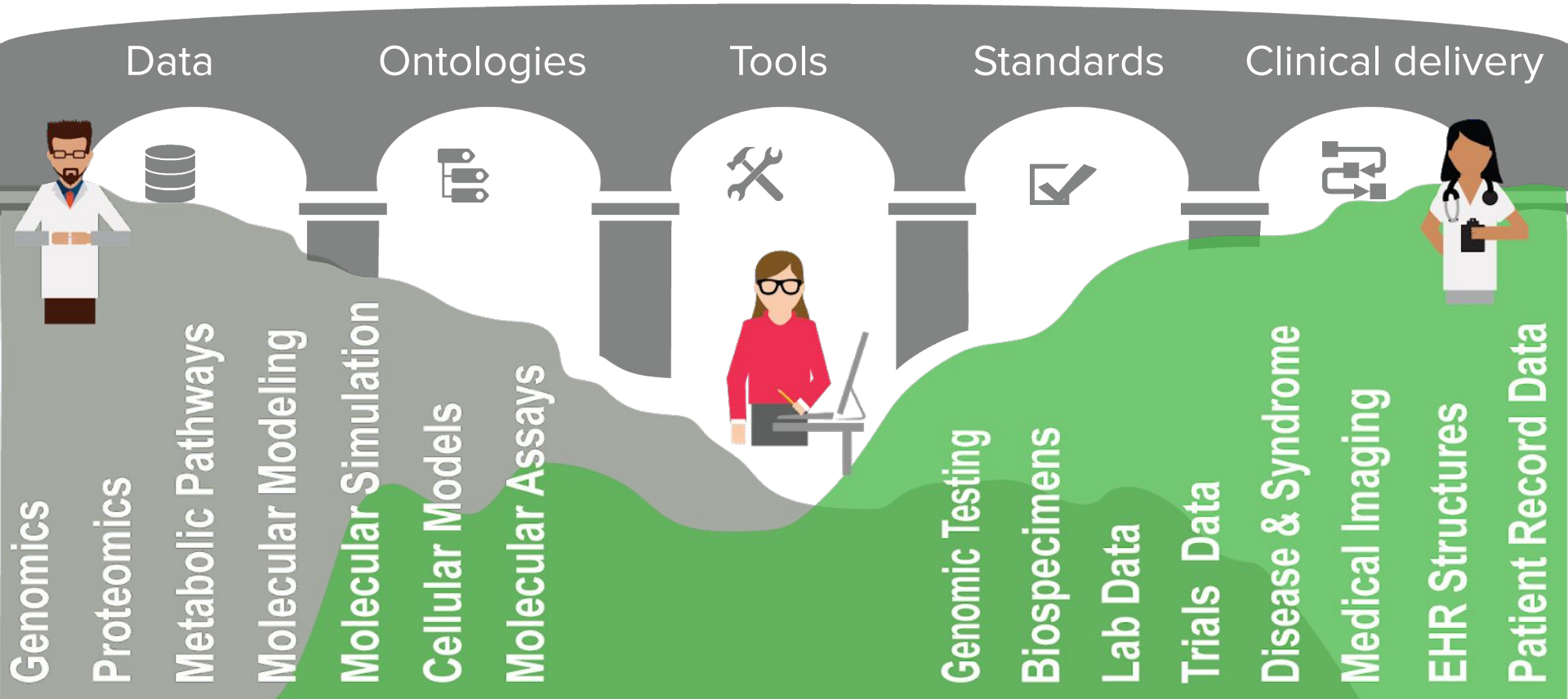
Unified Human Data

Development of ontologies and design patterns

Tools, web services, visual widgets

E.g.,: Phenopackets

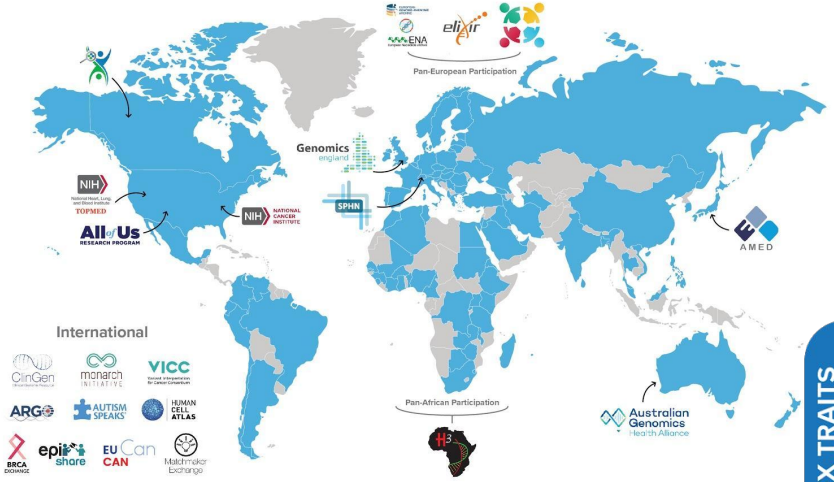
A bridge to the clinic

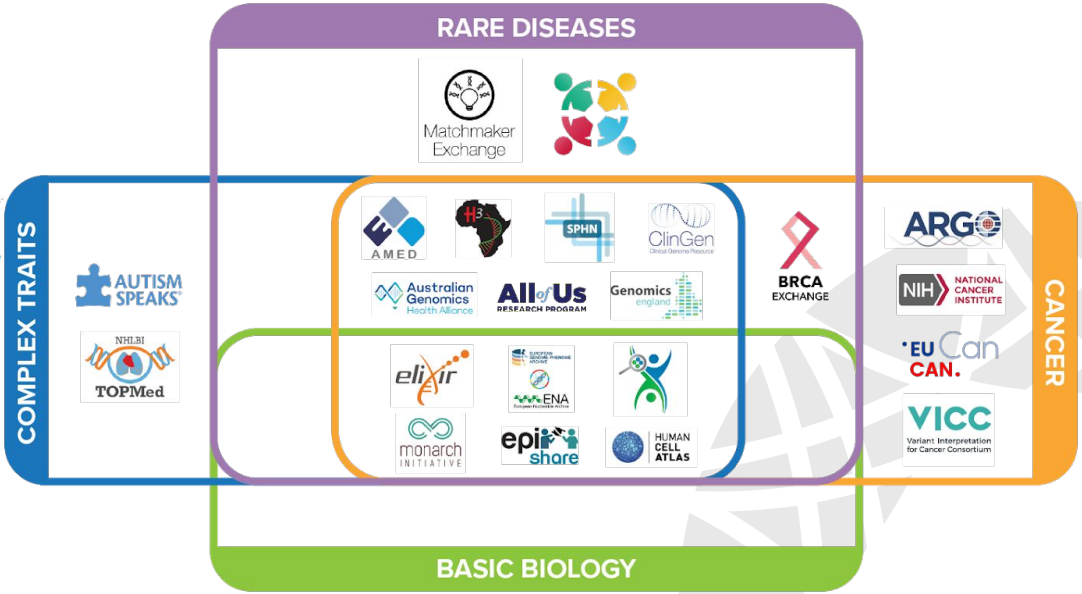


Global Alliance for Genomics & Health (GA4GH)

www.ga4gh.org

GA4GH aims to accelerate progress in genomic science and human health by developing standards and framing policy for responsible genomic and health-related data sharing.





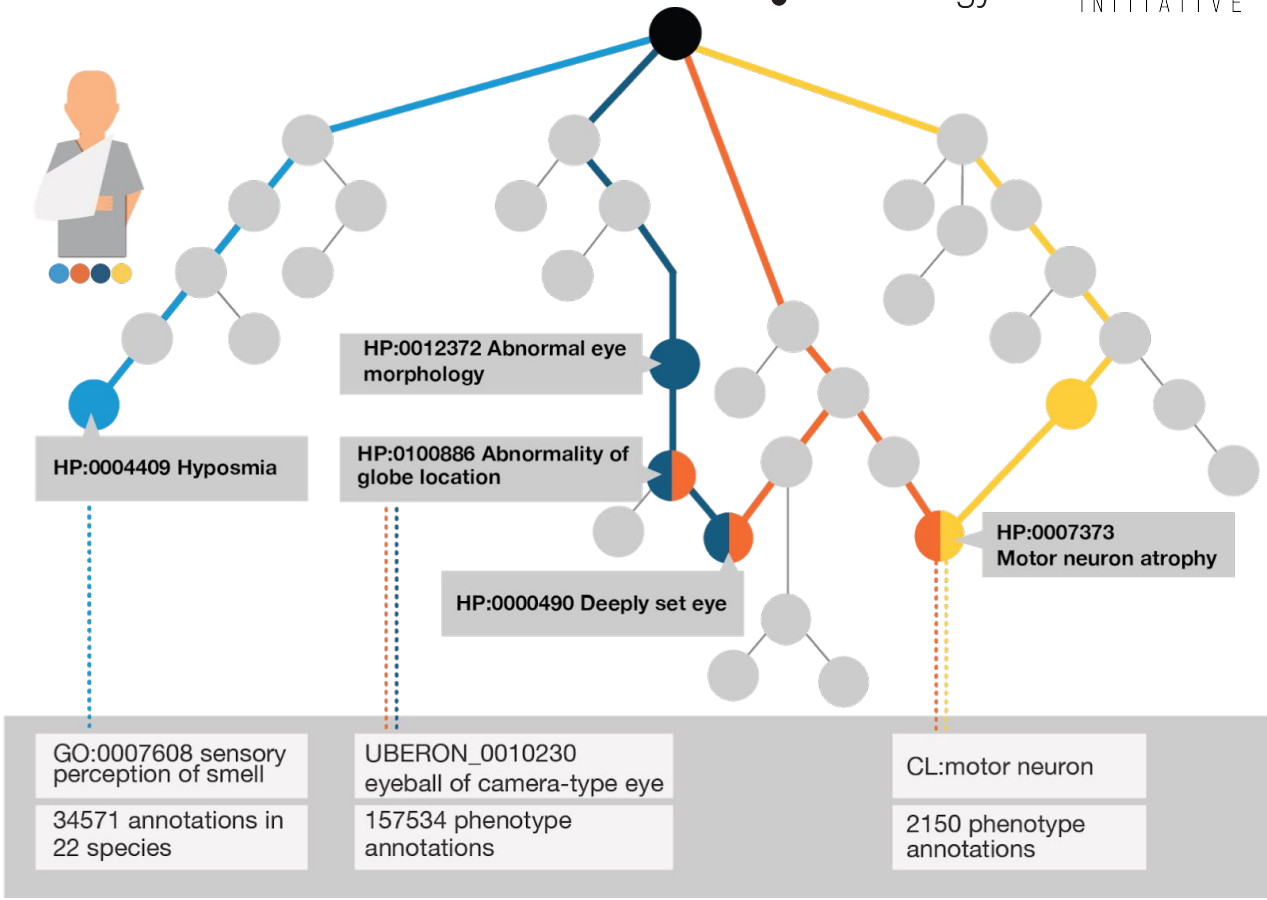
Global Alliance
for Genomics & Health

Collaborate. Innovate. Accelerate.

Human Phenotype Ontology (HPO)

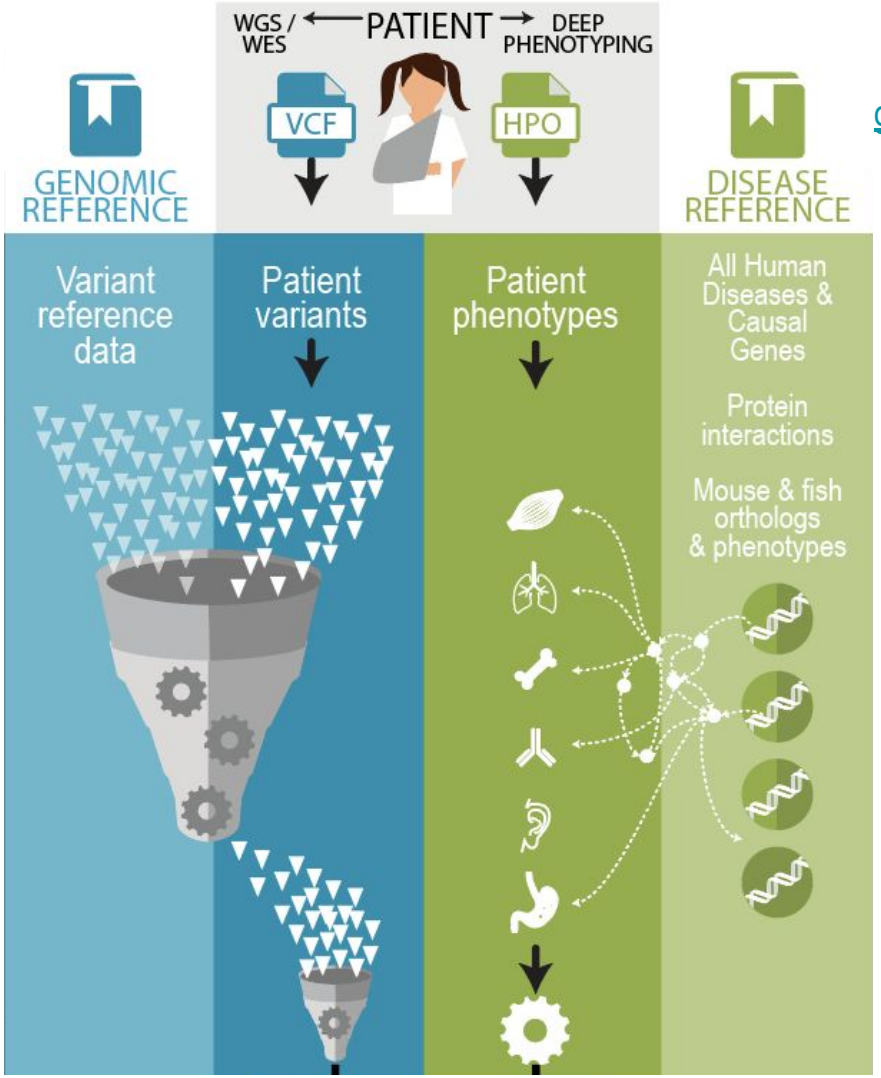
- **Phenotyping terminology**
  >14,500 terms
- **Computational disease models**
  >190,000 disease-phenotype annotations (associations)
- **Widely adopted in rare disease genomic diagnostic tools**
  100,000 Genomes Project, SOLVE-RD, NIH-UDP, etc.

hpo.jax.org



Combining genomic and phenomic data improves variant prioritization for diagnosis

doi: 10.1038/gim.2015.137



EXOMISER

github.com/exomiser/Exomiser

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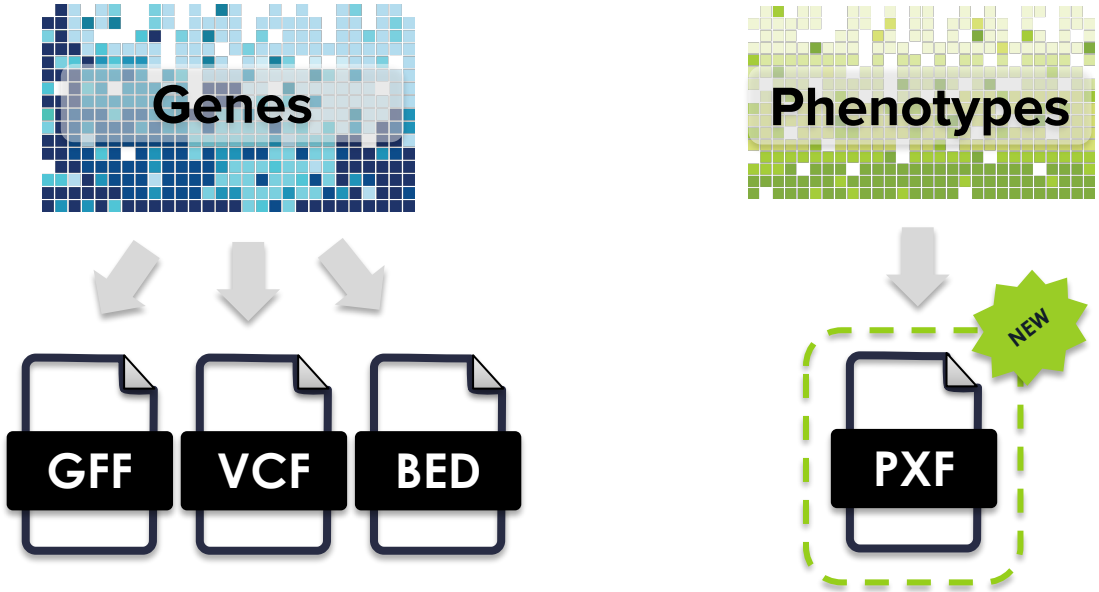
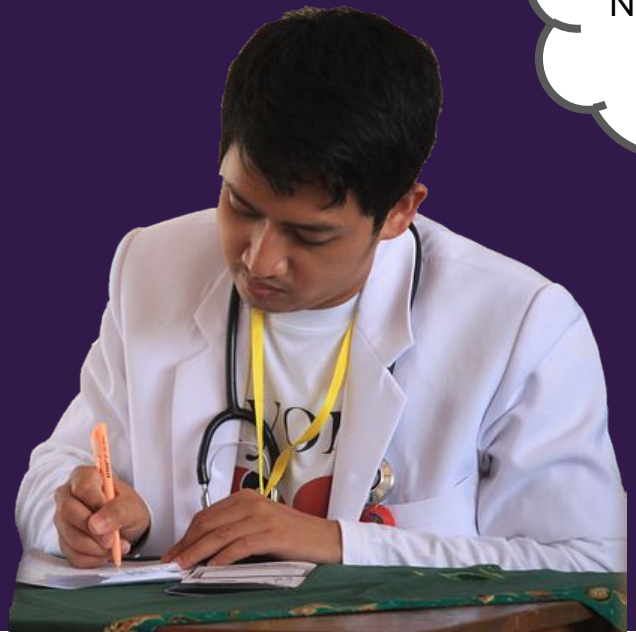
Standard exchange formats exist for sequence/genomes but not for phenotypes



We need a standard way to share case-level phenotypic information that is not free text, a candidate diagnosis proxy, nor full EHR data exported via PDF

Phenopackets can help us do better

Craniosynostosis
Brachydactyly
Proptosis
Broad thumb...



Were they NOT observed?

How are these linked to a patient?
To genomic info?
To samples?
To parents and siblings?

How severe are these?

Are some more severe than others?

When were they first observed?

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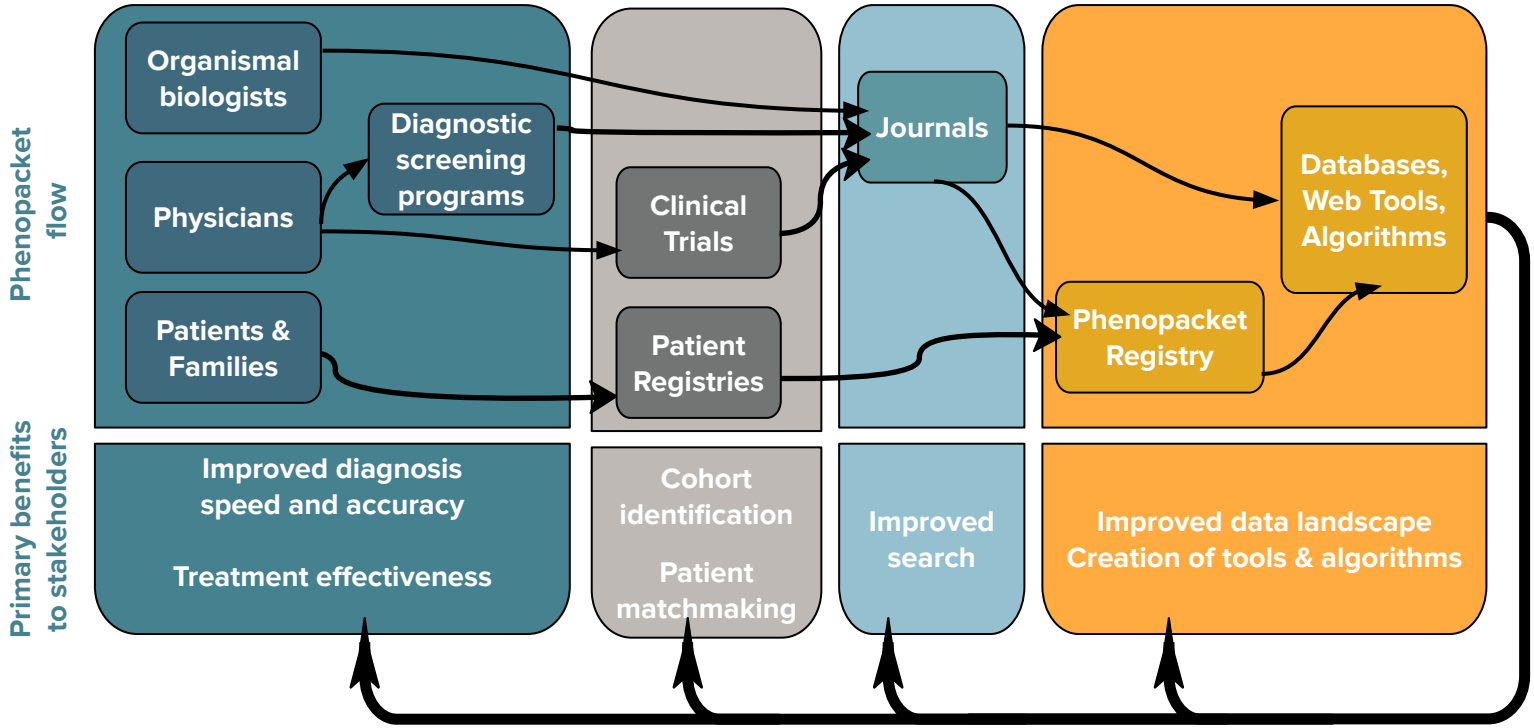
The Phenopacket Ecosystem

users and use cases



phenopackets.org

https://github.com/phenopackets

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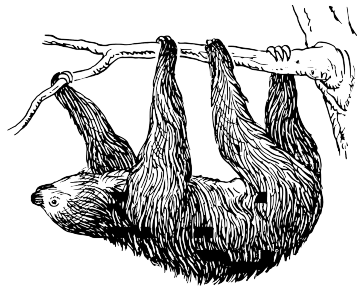
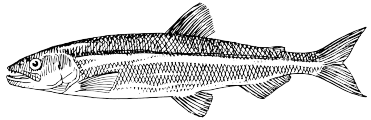
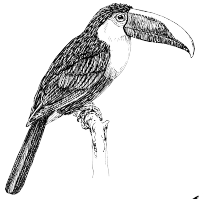
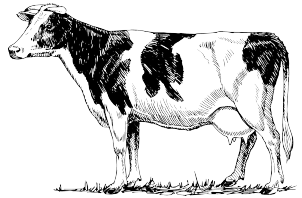
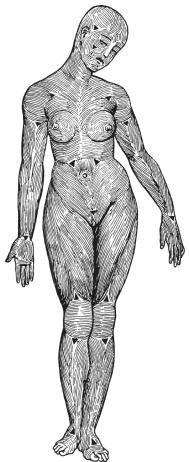
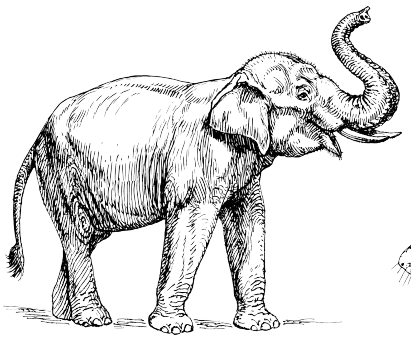



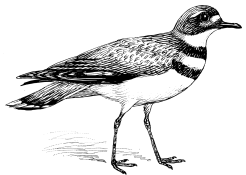
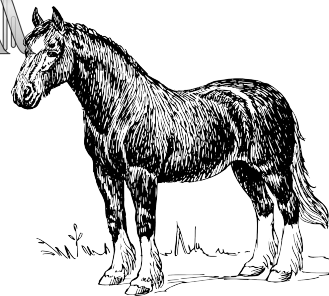



The Value of Cross-Species Research





Other species aren't just relevant; each has unique phenotypes

- The dog's retina has area centralis (analogous to the human macula) & fovea-like region, similar to humans; useful to study naturally occurring cone diseases

- Aged cats are natural models of Alzheimer's Disease: they form Abeta oligomers, neurofibrillary tangles, and have neuronal loss

- Naked Mole Rats don't get cancer

- Armadillos are a natural host of *M. leprae*, the mycobacterium that causes leprosy (only one besides humans)

- Tree shrews' glioblastomas are morphologically & genetically similar to humans (& more similar than mouse models)

- Great pond snails are models of inflammation-mediated memory dysfunction, and show evidence of spontaneous neural tissue regeneration after injury

- Silkworms are a model for uric acid metabolism. Decreases in plasma uric acid are correlated with clinical progression of Parkinson's Disease

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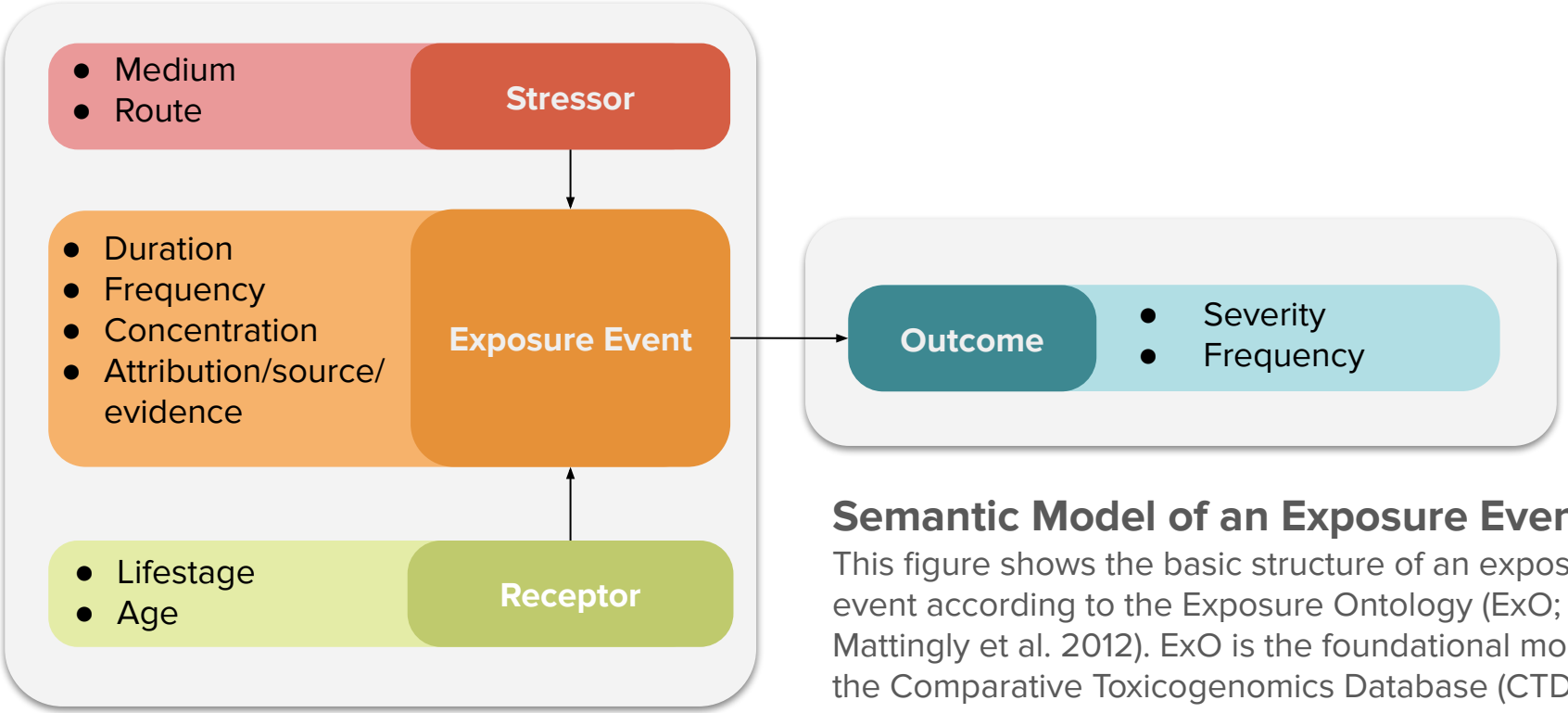
Environmental Exposures Modeling with ExO



Semantic Model of an Exposure Event.
This figure shows the basic structure of an exposure event according to the Exposure Ontology (ExO; Mattingly et al. 2012). ExO is the foundational model for the Comparative Toxicogenomics Database (CTD; Mattingly et al. 2006).

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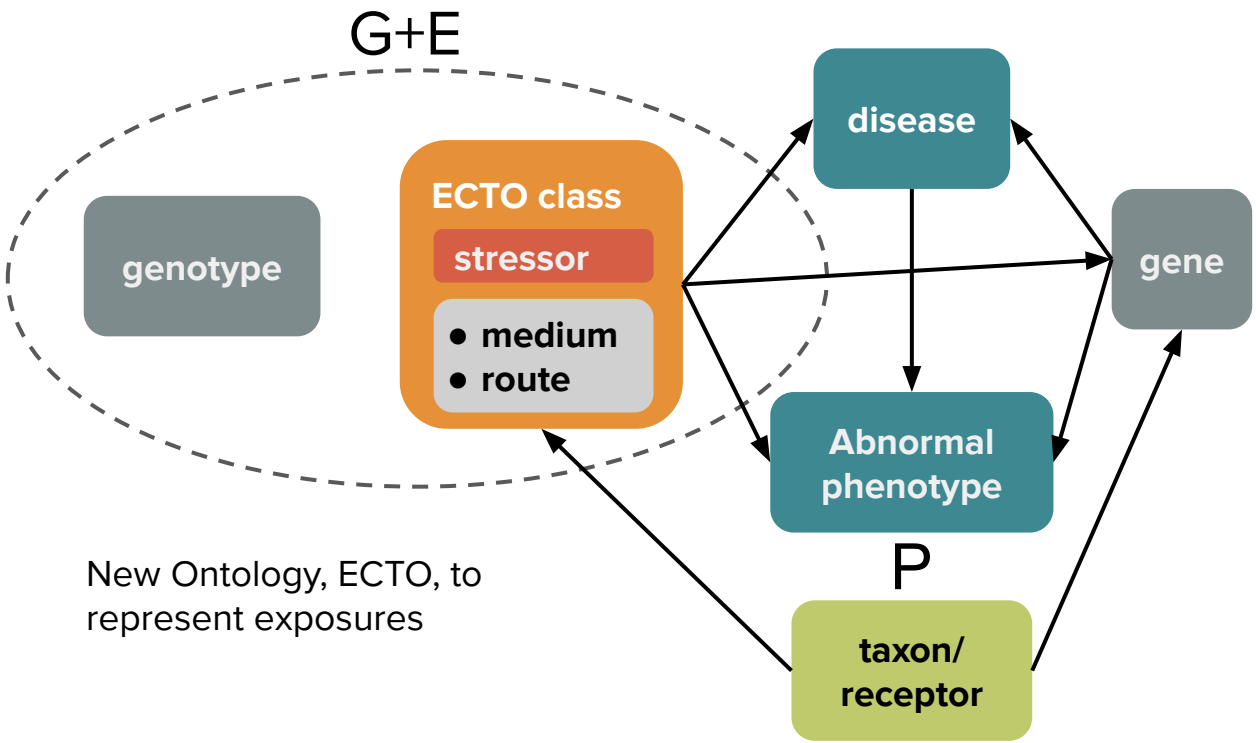
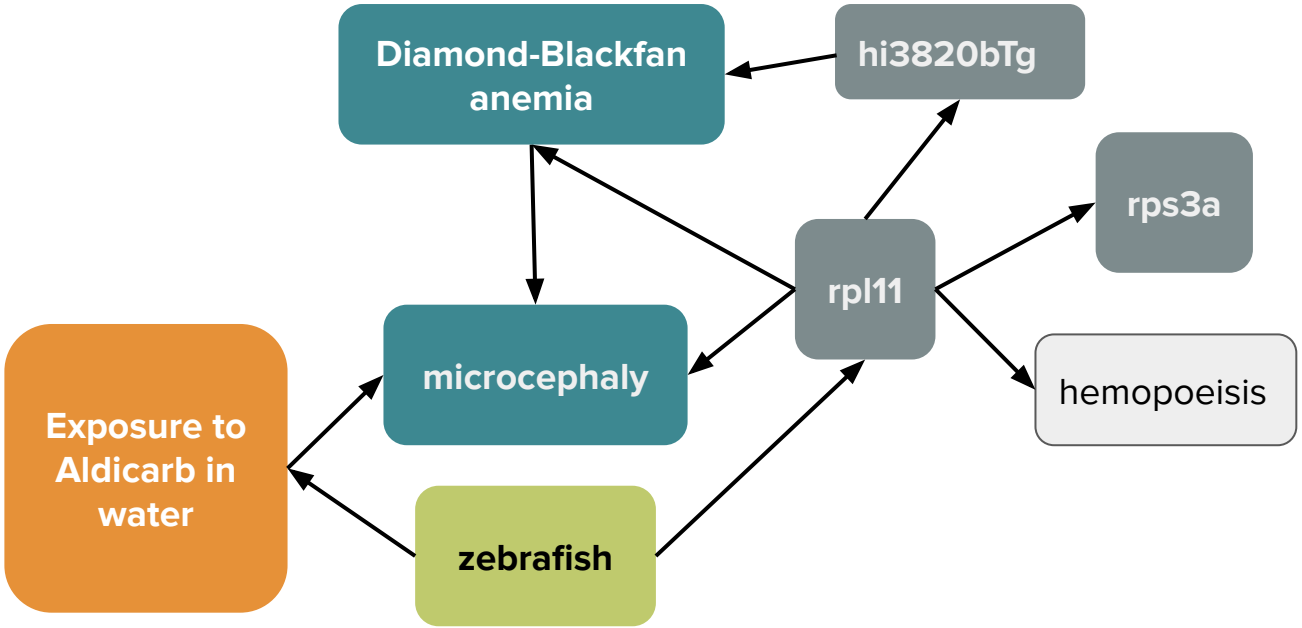
Integration with the Monarch Knowledge Graph



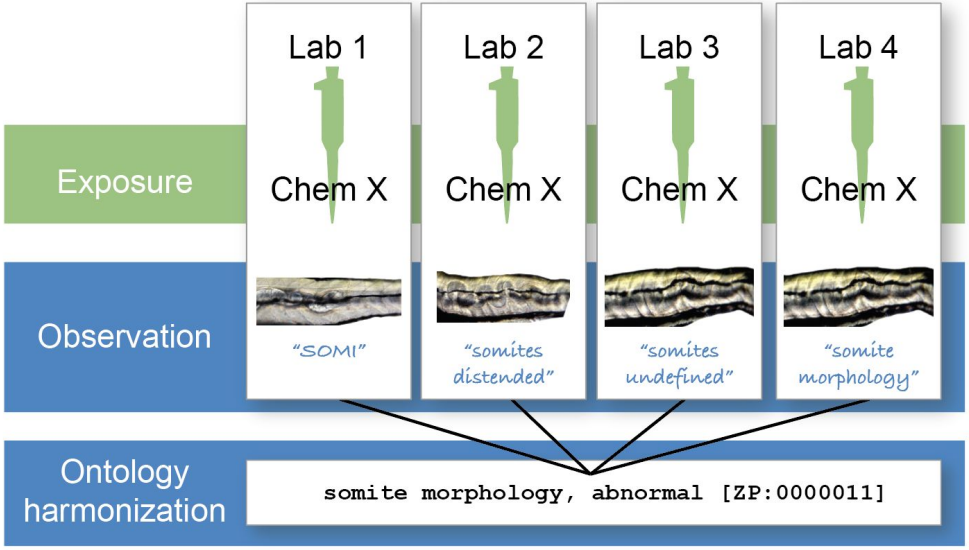
New Ontology, ECTO, to represent exposures

Integration with the Monarch Knowledge Graph



High Throughput Zebrafish Studies

- High-throughput zebrafish studies
- Quickly finding endpoints
- Labs use their own vocabulary
- Hinders data integration
- Ontologies are a potential solution
- Can we standardize endpoint reporting in a useful way?



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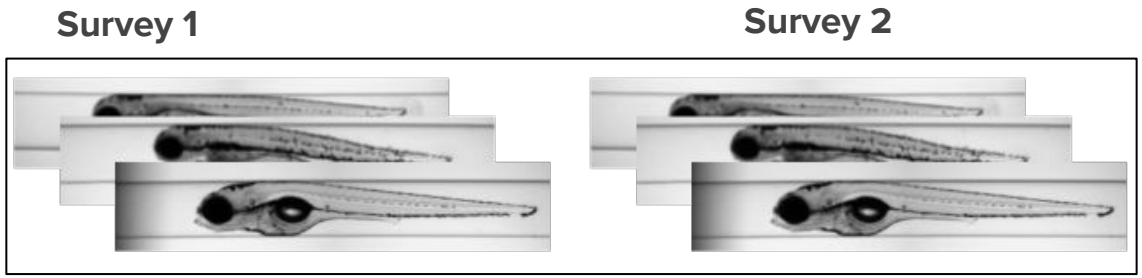
High Throughput Zebrafish Studies

- Annotators used 1,748 unique terms to describe 48 ZPO phenotypes
- Abnormalities of the gut, pectoral fin, and otic vesicles were most heterogeneously described
- Abnormalities of the heart and yolk were most consistently identified



RESULTS:

- Does everyone mean the same thing when they use the same term? **NO**
  For example, the term 'heart edema' often lumped many heart deformities.

- Is everyone scoring the same images with the same endpoints? **NO**
  In survey 1, annotators did not even agree on which embryos were normal

- Does using the ontology improve consistency across labs? **YES**
  Agreement between annotators was better when ontology terms were provided (Fleiss' Kappa for Survey 1 = 0.07 and Survey 2 = 0.11)

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Thank you

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