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GenomeDiver: A platform for phenotype-guided medical genomic diagnosis.

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CONFLICTS OF INTEREST

NSAH was previously employed at Regeneron Pharmaceuticals and has received an honorarium from Genentech. EEK has received speaker honoraria from Regeneron Pharmaceuticals and Illumina, Inc.

ETHICS DECLARATION

The NYKidSeq project ([ClinicalTrials.gov](https://clinicaltrials.gov/Identifier/NCT03738098) Identifier: NCT03738098) was approved by the Institutional Review Boards (IRBs) of Icahn School of Medicine at Mount Sinai and Albert Einstein College of Medicine. Informed consent was obtained from all study participants. All data were de-identified for downstream research, including the GenomeDiver user experience trial.

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Abstract

Purpose: Making a diagnosis from clinical genomic sequencing requires well-structured phenotypic data to guide genotype interpretation. A patient's phenotypic features can be documented using the Human Phenotype Ontology (HPO), generating terms used to prioritize genes potentially causing the patient's disease. We have developed GenomeDiver to provide a user interface for clinicians that allows more effective collaboration with the clinical diagnostic laboratory, with the goal of improving the success of the diagnostic process.

Methods: GenomeDiver uses genomic data to prompt reverse phenotyping of patients undergoing genetic testing, enriching the amount and quality of structured phenotype data for the diagnostic laboratory, and helping clinicians to explore and flag diseases potentially causing their patient's presentation.

Results: We show how GenomeDiver communicates the clinician's informed insights to the diagnostic lab in the form of HPO terms for interpretation of genomic sequencing data. We describe our user-driven design process, the engineering of the software for efficiency, security and portability, and examples of the performance of GenomeDiver using genomic testing data.

Conclusions: GenomeDiver is a first step in a new approach to genomic diagnostics that enhances laboratory-clinician interactions, with the goal of directly engaging clinicians to improve the outcome of genomic diagnostic testing.

INTRODUCTION

Compelling economic evidence now supports how genomic sequencing saves both money and time^{1,2} and improves quality-adjusted life years³ in the diagnosis of the 3.5–5.9% of the population with rare diseases.⁴ To make this genomic diagnostic process more efficient, substantial attention has been appropriately paid to detecting and understanding the effects of sequence variants in the human genome.⁵ Linking genetic variants to diseases is challenging and is most successful in case-control studies or when comparing multiple affected and unaffected family members, for which excellent analytical approaches have been developed.^{6,7} In a clinical context, however, testing can only be ordered on the proband and one or both parents (if available), with results needed sufficiently rapidly to influence care. The genomic diagnostic laboratory relies on linking the variants present in the patient's genome with the patient's phenotypic features. When a pathogenic genetic variant has previously been found to be the cause of a disease, that associated disease is characterized by a set of Human Phenotype Ontology (HPO) terms.⁸ If the patient has a variant that appears potentially pathogenic, causality is supported if the list of HPO terms in the disease associated with a pathogenic variant of that gene significantly overlaps the HPO terms used to describe the patient. A number of phenotype-based variant prediction tools exist to perform this kind of variant prioritization.⁹

If the diagnostic laboratory is provided with a greater number of HPO terms describing the patient on whom sequencing was performed, the diagnostic yield is increased.^{10,11} The comprehensive collection of these HPO terms is very difficult to scale effectively. Ordering genomic tests for rare diseases involves providing the lab with a primary indication for the testing (*e.g.* hearing loss, seizures), but also requires communicating additional findings in the patient, sometimes through checklists completed as part of the test order, also potentially involving the diagnostic laboratory reviewing notes from the patient's health record. The diagnostic laboratory staff then extract information from these sources and make decisions about how the phenotype can be represented as HPO terms. In critically ill children, an approach has been described that involves automated extraction of HPO terms from the electronic health record (EHR) using natural language processing,¹² helping with the speed of generation of HPO terms.

We have developed GenomeDiver as part of the NYCKidSeq project¹³ to help clinicians contribute more effectively to the diagnostic process. The NYCKidSeq project is jointly funded by the National Human Genome Research Institute and the National Institute on Minority Health and Health Disparities, and is one of seven national clinical projects that are part of the Clinical Sequencing and Evidence-generating Research consortium (CSER).¹⁴ GenomeDiver facilitates the curation of HPO terms by the clinician quickly, in greater numbers and more accurately than is currently typical, with the goal of improving our ability to make diagnoses using genomic information.

MATERIALS AND METHODS

The user-centered design process for GenomeDiver

We developed GenomeDiver using evidence-based participatory methods from design thinking.¹⁵ User research began with initial interviews with physicians and genetic testing laboratory staff, followed by a one-day stakeholder workshop and a design sprint to understand user needs, to define requirements, to sketch candidate workflows, to choose among them and to prototype. We included physicians (with and without specialist genetics training), genetic counselors, genetic testing laboratory personnel, research scientists, software tool builders, bioinformaticians and biologists, a designer, and a software engineer. The resulting concepts, sketches, and paper prototypes informed the designs for user experience, workflow, and user interfaces.

The GenomeDiver workflow: overview of a 'dive'

The workflow for a case (Figure S1) begins with the upload by the genetic testing lab of the patient's genomic information as a variant call format (VCF) file, along with the HPO terms that they derived from the test requisition documents. The clinician then starts a 'dive' by selecting the patient from the GenomeDiver interface. The next step, refining the patient's phenotype, requires the clinician categorize HPO terms generated by GenomeDiver by dragging each into one of three screen areas: 'Present' in the patient, 'Absent', or 'Unknown'. Using this updated and enriched phenotypic information, GenomeDiver re-analyzes the genomic data and presents candidate genes and associated diseases for the clinician to review and flag, adding any comments that they would like to communicate to

the diagnostic laboratory. To conclude the workflow, the updated HPO term categorizations, flagged diseases, clinician comments and the re-ranked shortlist of variants are returned to the diagnostic laboratory for interpretation.

Variant prioritization and reverse phenotyping to select HPO terms

We illustrate the variant prioritization steps in Figure S2. The VCF and starting HPO information are used for an Exomiser¹⁶ analysis. Exomiser is a gene prioritization tool that combines a score quantifying the likely pathogenicity of a variant associated with a gene (variant score) with a second score that measures the similarity of the phenotypic features of the patient with those associated with a pathogenic variant of the gene (phenotype score). Both values are used to generate the combined score for the variant. GenomeDiver interacts with Exomiser by using Exomiser as a source of prioritized genes, and by feeding back enhanced HPO information to help Exomiser refine its predictions.

We describe the prioritization and filtering steps in detail in the Supplementary Information. An Exomiser run is initiated based on the patient's VCF and the HPO terms from the test requisition. This generates a list of variants, each of which is associated with a gene. Each gene in turn is associated with one or more diseases, and these individual diseases are described by sets of HPO terms. We collect the HPO terms for the genes that Exomiser has ranked highest for causing the patient's phenotype. These are filtered for redundancy, focusing on those that are descendants of 'Phenotypic abnormality' (HP:0000118), and those associated with the specific disease prioritized by Exomiser. This leaves a subset of HPO terms that go through multiple rounds of selection, with the goal to present to the clinician 5 non-redundant HPO terms associated with each candidate gene, generating a maximum of 25 new HPO terms for categorization.

Re-analysis based on enriched HPO information and disease exploration

A further potential input by the clinician is made possible by re-running Exomiser, now updated with the newly categorized HPO terms that are used by Exomiser to generate revised combined scores. GenomeDiver then presents the clinician with a list of genes ranked by the absolute combined score, displaying the magnitude and direction of change of the scores, and linking to associated candidate diseases. The hyperlink embedded with the names of each candidate disease brings the clinician to a description of the disease, letting them judge whether the syndrome of features plausibly fits their patient. Any disease of interest can be flagged, with the final step of the dive involving the clinician returning the list of updated HPO terms, any flagged diseases and free text comments as a file for the diagnostic laboratory.

User experience trial

We performed a user experience trial of the software with four of the NYCKidSeq clinicians, none of whom had used the software previously. Six NYCKidSeq patients lacking a final genomic diagnosis were selected, and the clinical synopsis generated on each from medical records was provided to each clinician. An initial user survey was performed to learn about prior GenomeDiver experience and current practice when communicating with genomic

diagnostic laboratories. The time spent at each stage of GenomeDiver interactions was recorded, followed by an exit survey, in which users were asked to evaluate their experience.

Software system architecture

We provide a detailed description of the GenomeDiver software in the Supplementary Information section.

RESULTS

GenomeDiver performance with simulated data

A video of the diagnostic laboratory interaction with the interface to set up a patient in the GenomeDiver system appears as Supplementary Video 1. Once set up, this allows a clinician to access the separate interface shown in Figure 1 for categorization of HPO terms. The upper section ‘Add Phenotype Feature’ allows text to be entered, prompting HPO terms as a dropdown list for selection by clicking. The design is intended to focus the clinician on the middle section to ‘Classify All Phenotype Features’, dragging and dropping individual HPO terms into categories of ‘Present’, ‘Absent’ or ‘Unknown’. After all terms have been categorized, the ‘Submit’ button on the bottom right activates and the updated information is sent back to GenomeDiver. This interaction appears in Supplementary Video 2.

We used the VCF for the publicly-available NA12878 genome,¹⁷ adding a variant of uncertain significance in the *FBNI* gene (ClinVar accession VCV000200085.4, NM_000138.4(FBN1): c.6449G>T(p.Arg2150Leu)). To simulate a request for analysis of a patient presenting with a clinical suspicion of Marfan syndrome (OMIM 154700), we used HPO terms for ascending tubular aorta aneurysm (HP:0004970), scoliosis (HP:0002650) and arachnodactyly (HP:0001166) as those potentially used in a test requisition in a clinical scenario.

We detail each step of the process of variant and gene filtering and prioritization in the Supplementary Information section (Figure S2), as well as the selection of HPO terms for presentation to the clinician (Figures S3–S4). For this particular combination of genomic and phenotypic information, two genes were selected, *FBNI* and *SKI*, the latter implicated in Shprintzen-Goldberg syndrome (OMIM 182212), whose phenotypic features likewise include aortic aneurysm, scoliosis and arachnodactyly.¹⁸ The HPO terms presented to the clinician are listed in Supplementary Table 1. We show how each term in our sample case was categorized in Supplementary Table 1 and illustrate how a second Exomiser run presents candidate diseases in Figure 2 (using steps illustrated in Figure S5). Of note, GenomeDiver never exposes information about variants to the clinician, preventing the clinician from bypassing the formal laboratory diagnostic reporting process.

User experience trial results

The time spent categorizing HPO terms is shown in Figure S6. The median time spent in categorizing HPO terms across the six patients was 203 seconds (3 minutes and 23 seconds). Categorization tended to be concordant between users (Figure S7). The subsequent interaction evaluating candidate genes and diseases took 134.5 seconds (2 minutes and

14.5 seconds) per case (Figure S8). Exit survey data revealed overall positive responses to the use of GenomeDiver, particularly for interface intuitiveness, speed and satisfaction in contributing to the diagnostic process (Figure S9), with all users reporting that they could foresee using GenomeDiver in their clinical practice.

DISCUSSION

In this initial deployment of GenomeDiver, we have focused on improving the diagnostic process when performing genome-wide (exome, genome) sequencing in the diagnosis of rare diseases. We recognize that we can potentially improve both the rate of successful diagnosis and decrease the time spent by diagnostic laboratory personnel if we can facilitate the provision of the HPO terms that are most likely to discriminate the highest ranked gene candidates for causing the patient's disease. With the appreciation that clinician time is limited, the interface is designed to be simple and intuitive, limiting the number of candidate HPO terms so that the entire categorization session lasts no more than a few minutes per patient, validated by our user experience pilot testing. The second stage of input, facilitating the exploration of diseases that could be affecting the patient, permits further clinician insights to be provided, this time studying the syndrome of phenotypic features in candidate diseases. These steps of identifying individual phenotypic features and then considering how they might aggregate in diseases and syndromes reflect reasonably accurately the typical clinical genetics evaluation, but with the added intent of contributing to the laboratory diagnostic process. While we present our choices for variant and HPO prioritization in the current version, these are intended to serve as the basis for the initial, functional version of GenomeDiver, but with the goal of incorporating community input for algorithmic improvement over time.

It is likely that HPO term harvesting from sources like EHRs¹⁹ and image analysis²⁰ represents an area of innovation that will expand over time. A value of the GenomeDiver interface is that it allows a clinician to assess whether candidate terms gleaned from diverse, automated sources are actually present in a patient, creating the potential that GenomeDiver can act as a clearinghouse for downstream curation of candidate phenotypic features. The categorization of HPO terms as 'absent' is not yet used by Exomiser, but the updated LIRICAL approach, based on a likelihood ratio framework that includes information about HPO prevalence data,²¹ can exploit such information and will be served by this functionality within GenomeDiver.

Several lessons from the user experience trial will be valuable for guiding ongoing development of GenomeDiver. Manual addition of HPO terms was an option chosen by one of the users, associated with significantly longer interaction with the software. As this is an option, not a requirement for progressing with a dive, this decision is at the discretion of the user, but it would be good to be able to make it more time efficient. The HPO term harvesting described above is likely to overcome some of the challenges of manual curation, but will increase the number of HPO terms for categorization, which was correlated with a prolonged duration of time interacting with the software (Figure S6). To address this, we will need to provide a way of presenting or prioritizing terms with the highest information content, and consider interface improvements to allow even more rapid categorization of

terms. We also need to understand non-concordance of HPO term categorization. On a positive note, we find it reassuring that the software does not constrain users into uniform decisions. With more use in a production setting, we will be able to study how inter-user variation is associated with success in diagnostic outcomes, allowing us to identify less productive interactions with the software, which can in turn prompt redesign to promote more effective interactions.

GenomeDiver may find uses beyond initial diagnoses of patients with a rare disease. GenomeDiver can facilitate re-analysis of patients with initially uninformative results whose phenotypes may have changed over time, and whose genomic variants may have undergone re-classification. GenomeDiver is fundamentally a tool to prompt ‘reverse phenotyping’ – checking whether specific phenotypic features are present in a patient based on their genotype. As such, GenomeDiver can serve clinicians not trained in clinical genetics or dysmorphology. With the development of HPO terms that now also encompass common diseases,²² GenomeDiver’s potential value as a reverse phenotyping tool that generates a genotype-based differential diagnosis could accordingly extend to much of medical genomics.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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DATA AVAILABILITY

The GenomeDiver software is available at <https://github.com/GenomeDiver/>. The patient genomes and HPO terms used in the user experience trial will be available as part of the Clinical Sequencing Evidence-Generating Research (CSER) data deposition on the Analysis, Visualization, and Informatics Lab-space (ANViL, anvilproject.org).

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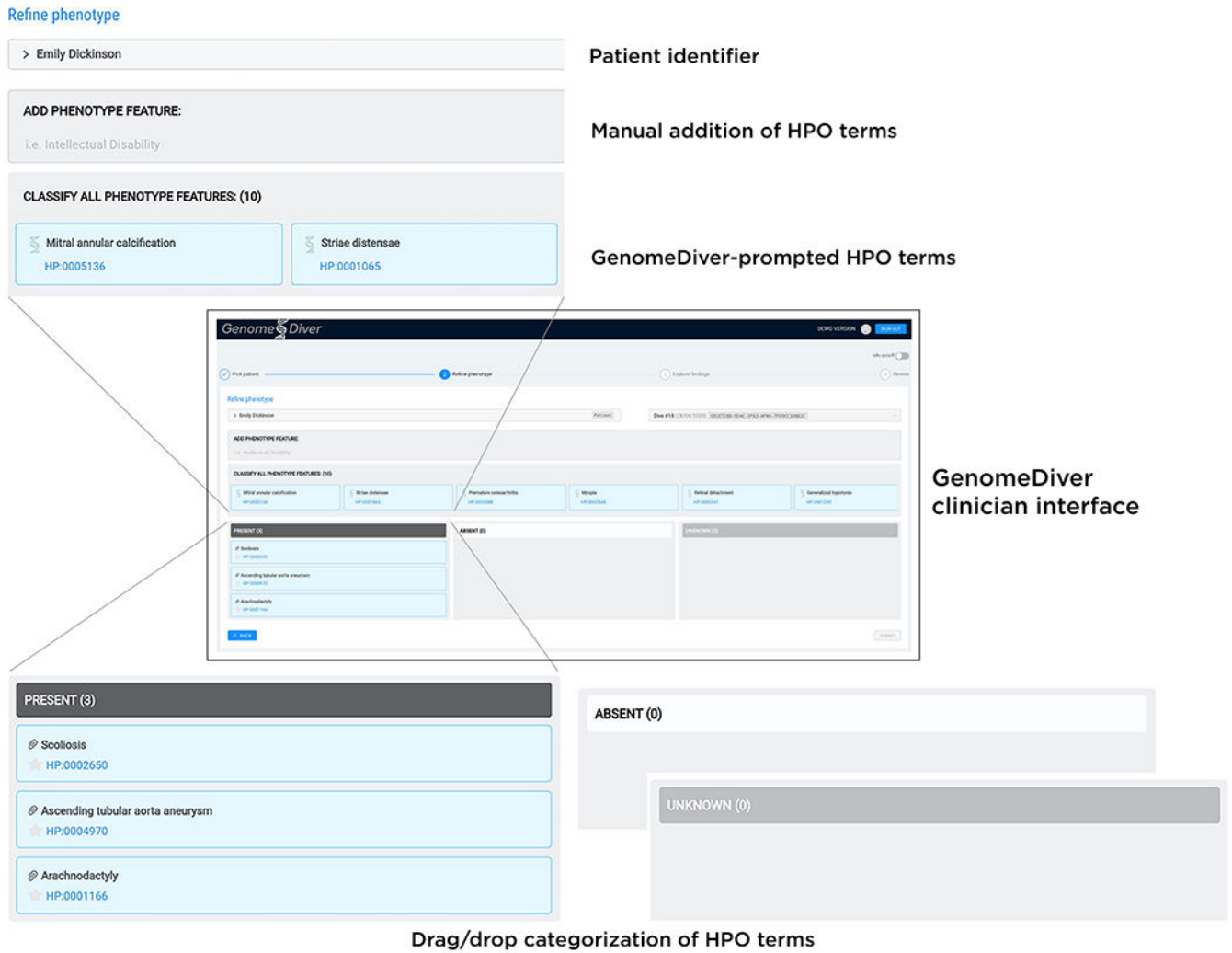


FIGURE 1:

The clinician interface for GenomeDiver. HPO terms can be added in the ‘Add Phenotype Feature’ field by entering text which will bring up a list of HPO terms from which the appropriate term can be chosen. The HPO terms generated by GenomeDiver are shown in the ‘Classify all phenotype features’ section. These can be dragged into each of the categories underneath, ‘Present’, ‘Absent’ or ‘Unknown’. Three terms have been moved into the ‘Present’ category as an example.

Gene/disease exploration interface

Flag any disease(s) likely fitting your patient

Gene	Score (Change)	Flag?	Disease	Explore Disease
FBN1	0.9965 (+0.0032)	<input type="checkbox"/>	Marfan Syndrome; MFS	OMIM:154700
TGFB2	0.9149 (-0.0669)	<input type="checkbox"/>	Loeys-Dietz Syndrome 4; LDS4	OMIM:614816
COL5A1	0.8874 (-0.0723)	<input type="checkbox"/>	Vascular Ehlers-Danlos Syndrome	ORPHA:286

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FIGURE 2:

Following the categorization of the HPO terms, a second Exomiser run re-prioritizes variants, genes and associated diseases. The clinician is presented with a shortlist of genes, ranked by the Exomiser combined_score which is shown, as well as the change in score (green positive, red negative) resulting from the HPO term categorization. We list the disease and a link that allows the clinician to explore whether a disease description resembles their patient, allowing them to flag one or more as being candidates for causing the patient's presentation. Free text can be used in the 'Add comment' box, finalizing the process by clicking 'Confirm analysis' to return the information to the diagnostic laboratory.