Dynamic software design for clinical exome and genome analyses: insights from bioinformaticians, clinical geneticists, and genetic counselors

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ABSTRACT

Background The transition of whole-exome and whole-genome sequencing (WES/WGS) from the research setting to routine clinical practice remains challenging.

Objectives With almost no previous research specifically assessing interface designs and functionalities of WES and WGS software tools, the authors set out to ascertain perspectives from healthcare professionals in distinct domains on optimal clinical genomics user interfaces.

Methods A series of semi-scripted focus groups, structured around professional challenges encountered in clinical WES and WGS, were conducted with bioinformaticians (n = 8), clinical geneticists (n = 9), genetic counselors (n = 5), and general physicians (n = 4).

Results Contrary to popular existing system designs, bioinformaticians preferred command line over graphical user interfaces for better software compatibility and customization flexibility. Clinical geneticists and genetic counselors desired an overarching interactive graphical layout to prioritize candidate variants—a "tiered" system where only functionalities relevant to the user domain are made accessible. They favored a system capable of retrieving consistent representations of external genetic information from third-party sources. To streamline collaboration and patient exchanges, the authors identified user requirements toward an automated reporting system capable of summarizing key evidence-based clinical findings among the vast array of technical details.

Conclusions Successful adoption of a clinical WES/WGS system is heavily dependent on its ability to address the diverse necessities and predilections among specialists in distinct healthcare domains. Tailored software interfaces suitable for each group is likely more appropriate than the current popular "one size fits all" generic framework. This study provides interfaces for future intervention studies and software engineering opportunities.

Keywords: exome, decision support systems, clinical, software design, genomics, medical informatics, cognitive science

RESEARCH AND APPLICATIONS

INTRODUCTION

As the cost of DNA sequencing continues to decrease, whole-exome sequencing (WES) and whole-genome sequencing (WGS) have become important clinical tools for identifying deleterious alleles in Mendelian and complex diseases.[1,2] Since its introduction in 2009,[3] more than 1980 papers highlighting WES clinical uses have been published (see Supplementary S1 for a brief comparative overview contrasting WES/WGS with other clinical genetic tests). However, the effective realization of moving WES and WGS from research to routine clinical practice remains challenging, in part due to the need for non-computational clinicians to analyze and interpret the large-scale data in a time efficient manner.[4–6] At this early stage, clinical access to WES/WGS analysis occurs principally on a research basis in academic health research centers where informatics teams are available to assist with data analysis.[7] As the utility of WES/WGS analysis increases and costs decline, the transition from bench to bedside will require new generations of genome analysis software to empower genetics professionals to perform clinical interpretation.[8,9]

The prospect of full genome sequencing, compounded by the continual growth in genetic knowledge base, is overwhelming for the healthcare professional; computerization for interpreting and acting on this information is essential for clinician support and ultimately patient care.[10] The capacity of software to assist a specialist in reaching a diagnosis (defined as "a contextual, continuous, and evolving process, where data are gathered, interpreted, and evaluated in order to select an evidence-based choice of action"[11]) is dependent on appropriate design and attaining a high level of usability. Careful evaluations of health information technologies are necessary to ensure sufficient system efficiency, effectiveness, and satisfaction for target users, minimizing workflow interruptions, unnecessary cost, and healthcare errors.[12–15] For research-focused WES/WGS analysis, distinct software architectures with different engineering emphasis have been introduced, all ultimately sharing the same goal to assist in the identification of key gene(s)/variant(s). The nature of the analysis process includes 5 steps: (1) read mapping of short DNA sequences onto a reference genome, (2) identification of differences between the sample and reference, (3) quality control of candidate variants (including data visualization methods), (4) annotation of the properties of observed variations, (5) prioritization or filtering variations as candidates for the observed phenotype/disorder (reviewed in[7,16]). Existing software programs address differing portions of the analysis process, with emphasis tending to fall either on categories 1-2, 3-4 or 5 (example software discussed in Supplementary S1).

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Many of the early WES/WGS software packages placed greater emphasis on the computationally oriented users, as clinical use was rare.[17,18] In a previous study of a cohort of clinical geneticists, we evaluated the usability of exome analysis software based on think-aloud protocols in a study where participants were presented with simulated clinical cases to analyze.[19] While our results highlighted deficiencies of the software for clinical geneticists, such users rarely work in isolation. An interdisciplinary team comprising of informaticians, clinical/biochemical geneticists, subspecialist pediatricians, laboratory scientists, and genetic counselors are often involved. This is exemplified by 2 programs at the National Institutes of Health (Clinical Sequencing Exploratory Research and Clinical Center Genomics Opportunity), seeking to bring together clinicians, genomic researchers, bioinformaticians, and ethicists to tackle challenges in WES/WGS analysis.[20,21] Despite the expectation of the groups working together, presumably through a shared computational framework, the diversity of perspectives, and preferences regarding software design remains undetermined. As the community moves to adoption of WES/WGS as a standard clinical test, it is unclear if the design of analysis software needs to be tailored to domain-specific users.

As far as we are aware, this work represents the first research looking at cognitive insights between distinct domains of medical professionals that most closely interact with genomic data. We surveyed three major groups of specialists that most closely interact with genomic data at the patient-oriented level: data-intensive informatics specialists (a newly emerging clinical role), clinical geneticists, and genetic counselors. In this report, we specifically addressed 3 key research questions:

1. Are there major cognitive differences and patterns among different user groups?;
2. What do the optimal designs envisioned by informaticians, clinical biochemists, and genetic counselors look like?3) How do the designs desired by the different user groups compare with existing designs?

Bearing in mind of the broad range of clinical applications of genomic data, we focus our research questions primarily in the context of difficult to diagnose germline rare diseases, or diseases with suspected genetic etiology. Through narrative discussions and digital prototypes, we revealed major patterns that distinguish between classes of specialists. We identified properties perceived by users to play a critical role in determining efficacy and efficiency of an analysis software. The results of the study will inform clinical interface design as WES/WGS move into the mainstream.

METHODS

Setting

All focus groups were conducted in the Child and Family Research Institute at BC Children's Hospital in Vancouver, Canada. Sessions were conducted within a conference room with a round table, chairs, a white board with markers, a video recorder (a mounted Sony HandyCam High definition camcorder (HDR)-SR1 + ECM-HW1R Wireless Microphone), and a digital projector connected to a Macbook Pro laptop.

Recruitment

Participants were recruited from across various institutions located within the greater Vancouver region. Twenty-six individuals from 4 different healthcare professions were recruited; each individual was categorized into 1 of the 4 user classes: bioinformatician, clinical geneticist, genetic counselor, and nonspecialist physician (see Supplementary S2). The first 3 user groups represent the current healthcare professionals that most closely interact with patient genomic data for clinical decision-making in precision medicine (we define precision medicine as "the ability to tailor diagnostic and treatment decisions for individual patients," see[8]). The last group (general physicians) represents the baseline within clinicians that do not have experience working with genomic data.

Focus groups assignment

Each homogenous focus group consisted of participants from the same professional category, and group sizes ranged from 4 to 5. There was no overlap between the group assignments such that each individual participated only once in a focus group. The participants for each group were randomly assigned. The focus groups were conducted in 2 rounds: 6 first-round sessions took place between February and June of 2014, and 6 second-round sessions took place between September and October of 2014.

Focus group structure

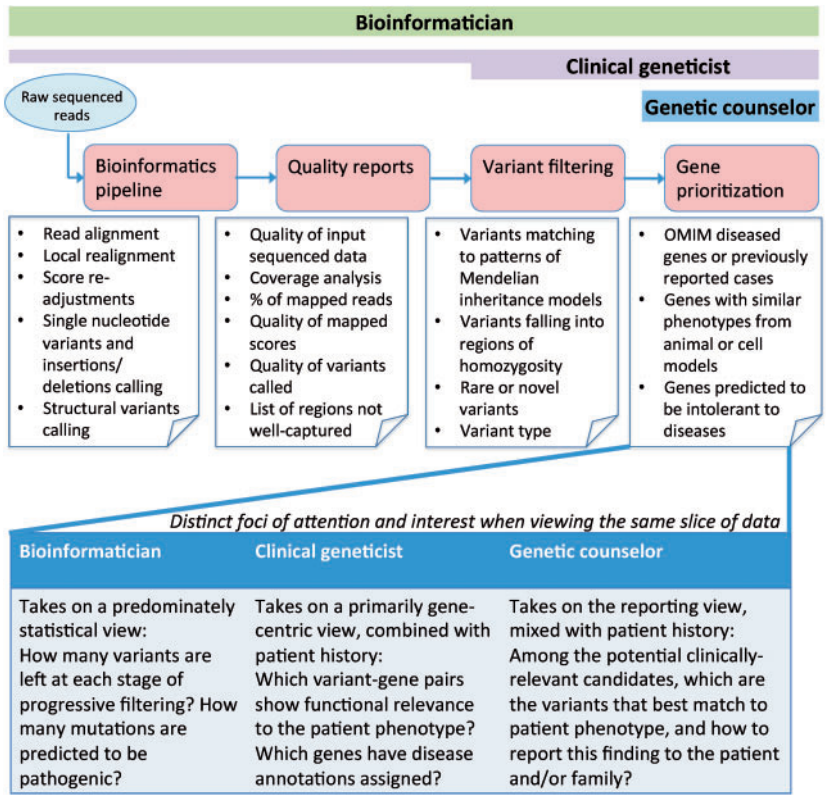
Participants filled out a demographic survey and consented by signing a project participation form at the beginning of each focus group session. Each focus group lasted between 90 and 120 min. The sessions were audio-recorded in their entirety and drawings made by participants on a whiteboard were digitally captured. Key matters that were repeatedly referred to in the focus groups were typed on a laptop by the moderator (Casper Shyr (CS)) and projected on a big screen via a projector. Throughout the session, participants had access to drinks and snacks.

The structure of the focus groups was built around the various processing stages of patient exome data (e.g., generation of alignment and variant calls, data annotation and visualization, variant/gene prioritizations). To guide the flow, many of the questions were structured around a hypothetical scenario involving a patient suffering from an undiagnosed rare metabolic disorder (see Supplementary S12 for discussion of study limitations), but participants were encouraged to think and discuss beyond the scenario. Some parts of the focus groups were scripted to raise issues including examining data quality and screening for technical and/or biological abnormalities, filtering exome variant calls at the genetic level, prioritizing mutations at the gene level, and smoothing out the technical challenges when collaborating across multiple researchers, and sharing the clinical findings with patients (see Supplementary S3 for more details).

Analysis

Focus group transcripts were generated from recordings and notes and coded in Microsoft Word. Content analysis was conducted to describe participants' views and perspectives on WES/WGS data.[22,23] A set of initial codes was formulated based on the research questions and prior studies.[19,24–26] Additional emergent themes and codes were identified from the data using an inductive approach.[27–29] The whiteboard drawings were analyzed from the video footages, and were digitally translated using GUI Design Studio Version 4.6. Themes and subthemes identified from the coded transcripts were used to highlight key features on the digital prototypes. Findings were summarized through tables, figures, and narrative discussion.

Figure 1: Beginning with raw sequenced reads, the exome analysis pipeline can be conceptualized into 4 distinct compartments: generation of alignments and variant calls, assessment of data quality, filtering of variants based on genetic models, and prioritization of genes based upon biological functions. The details of the components are annotated largely in the context of genetic diagnosis for rare/complex disorders (refer to Supplementary S12 for discussion on other clinical uses of genomic data). The bars above represent the intensity of user engagement at each step. Bioinformaticians preferred to be involved in every step, with equal attention devoted to all compartments. Clinical geneticist, despite placing heavier emphasis on the final 2 stages, indicated they would ideally like to be involved in every step too, but they faced difficulties in carrying out the first and second steps (e.g., pipeline execution and quality assessment), which may be attributed to software usability. Genetic counselors (and general physicians, not shown) indicated they would focus on the final output of candidate variants, to which they could apply their domain knowledge to select clinically relevant genes. The text in the lower portion of the figure highlights how the same step in the informatics pipeline (e.g., variant data) can be viewed differently across domain experts.



Approvals

This study was approved by the University of British Columbia Behavioural Research Ethics Board (H13-02034).

RESULTS

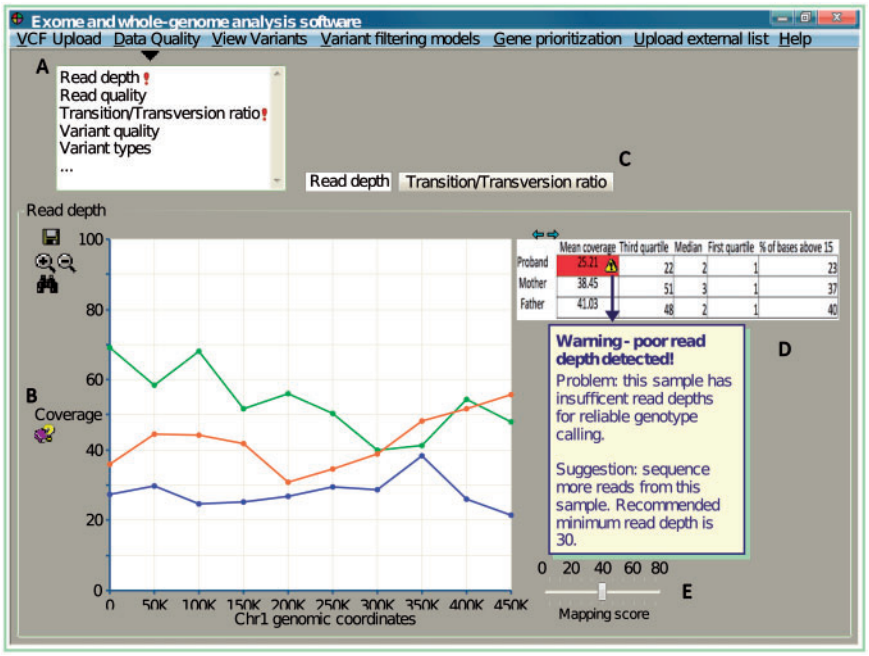
1. User groups demonstrate dissimilar focus in the analysis pipeline

The diverse WES/WGS analysis software tends to emphasize specific points in the analysis pipeline, in a package specific manner. We sought to understand whether the focal point of the software packages tends to reflect distinct user community desires. To ascertain preferential starting points in WES/WGS analysis, participants were asked to choose between working with raw unaligned sequenced reads, or to work with variants called with an external informatics pipeline. These 2 choices represent typical options offered by sequencing centers and commercial companies.[30,31] The preferences from each participant were immediately reflective of the domain they represented, and it was apparent that the same genomic data were treated differently by each of the 3 user classes (Figure 1).

Bioinformaticians desired to start with raw sequence data, but also indicated that having access to both raw data and externally provided variant lists would be ideal:

> *"I prefer to work with raw sequence data because it gives me greater flexibility. If I don't see any interesting candidate from my output, I can re-analyze the data using different thresholds, or try a different genome aligner, or a different variant caller. Having the variant calls is a bonus—I can go to the variants right away while the pipeline is still processing raw reads. This is especially important when I have multiple whole genomes where the processing time is expected to be long." [Bioinformatician 02]*
>
> *"Ideally I would like to have both [raw data and variant data]. But having the raw sequence data means I can go back and re-do the analysis as future algorithms improve, or as genome annotations get updated . . . or if I need to investigate other types of genetic variations like large structural inversions or deletions or duplications." [Bioinformatician 05]*

Figure 2: A graphical representation of key features desired by clinical geneticists for inspection of data quality. (**A**) Measurements associated with data quality should be grouped together into a common theme (e.g., a drop-down panel). Quality scores deviating from the norm should be automatically highlighted (e.g., exclamation mark). (**B**) Computational jargon (e.g., coverage) need to be appropriately explained to a noncomputational user. (**C**) Details on different quality measurements should be displayed separately, but still contained within the same user interface. The example here uses tabs to access different perspective views. (**D**) Data are best represented both visually (e.g., as a graph) and numerically (e.g., summarized in tabulated form). Simply presenting the quality metrics is not sufficient; software must further describe the nature of the problem, and provide recommendations. (**E**) The user needs flexibility to explore the distribution of quality scores, and visualize how different thresholds impact the data results. Here, a bar representing the mapping threshold is introduced for the user to dynamically adjust, and the expectation is the interface will update the coverage accordingly.



Similarly, clinical geneticists preferred both raw sequence data and variant calls, but with a stronger partiality for working with variant calls over raw reads because they believed working with the already aligned and annotated data gave them a better chance to identify clear causal variants quickly.

> *"If we are dealing with a recessive disorder, then mosaicism and de novo dominant models are less of a concern. I do not have to worry about twiddling different variant quality scores that is often so important when searching for bona fide heterozygous mutations." [Clinical geneticist 05]*
>
> *"Starting with only the variant data generally means that the data I am given has already been filtered by some kind of threshold so I am restricted to play within the limit of that threshold. I have yet to find a user-friendly interface that would allow a non-computer savvy clinician such as myself to process an exome data from beginning to end. For now, I am limited to getting only the final sorted list from the bioinformaticians." [Clinical geneticist 03]*

Genetic counselors and general physicians expressed no desire for raw sequences, indicating that they did not consider it as part of their professional role (Supplementary S4). There were also differences on the preferred file formats between bioinformaticians vs the geneticists and counselors (Supplementary S5).

2. Separate interfaces required for data quality assessment

A. Desired statistics

Participants were asked to discuss issues regarding quality examination of WES/WGS dataset(s).

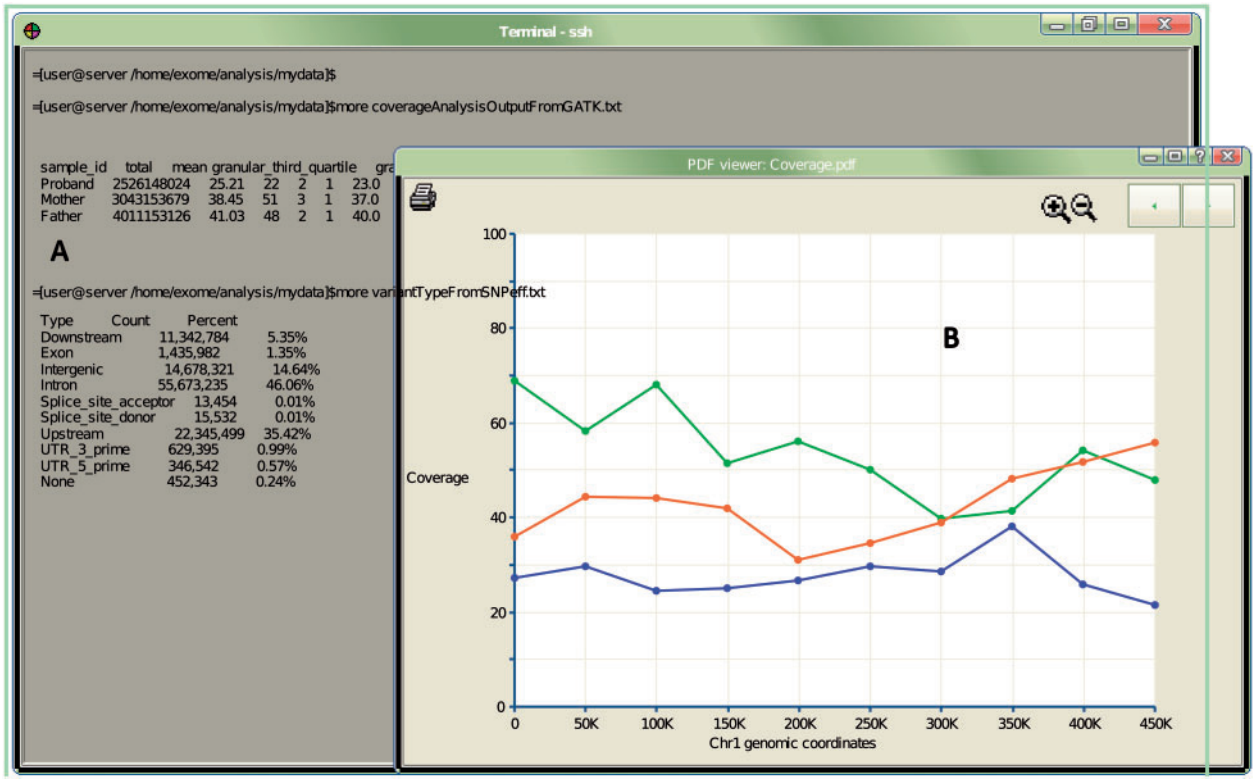
Genetic counselors and general physicians stated this entire topic was of no relevance to their line of work.

> *"I don't think it is up to me to inspect data quality. I don't even know where to begin! That is not what I am trained to do. When I receive the data, I expect it to have already been quality-checked." [Genetic counselor 02]*

There was a strong overlap between the bioinformaticians and clinical geneticists when commenting on the quality measures desired, and some mentioned quality measurements are not commonly available in current toolkits (Supplementary S6). Both user groups wanted to see a list of genes (or sub-segments of genes) whose exomes were not sufficiently covered, to compare against a list of genes relevant to their study.

> *"It is important for me to know what genes are included in a capture kit so if there is an insufficient coverage for a set of genes, I can decide if simply re-sequencing the data with the same platform would guarantee more reads at those locations, or if I need to explore alternatives like whole genome sequencing." [Bioinformatician 02]*

Figure 3: A graphical representation of key features desired by bioinformaticians. (**A**) Terminal interface is the most utilized environment, as it connects with many other command-line software and scripts. Tabulated data quality summaries are displayed directly on the terminal. (**B**) Graphical summaries are also desired, but no intensive graphical user interface app is needed, as bioinformatics users tend to prefer features already available via the terminal display.



"I want to know what genes are not sufficiently covered in my exome because currently, all that is given to me is a list of variants. From that list, if I don't see any mutations in those genes, I would be mistaken to think those genes are normal when they could be not." [Clinical geneticist 04]

B. Visual presentation

While the desired metrics and functionalities overlapped highly between the bioinformaticians and clinical geneticists, the preferred methods of presentation differed between them. Figures 2 and 3 outline the key differences.

3. Filtrations and prioritizations

A. Variant-level filtration

For genetic counselors and general physicians, there were few comments about filtering at the variant level. When the data reached their hands, they expected it to have been filtered based on specified genetic model(s) and allelic frequencies, allowing them to focus on prioritizing candidate genes.

We found a set of filters selected by both bioinformaticians and clinical geneticists, the majority commonly cited in the exome literature (e.g., sort alleles by allelic frequencies, mutation type, and impact prediction.[32,33]). The variants were preferred to be displayed within a table or spreadsheet—a design that is already implemented in many exome analysis systems.

In accordance with how they inspected data quality, bioinformaticians preferred to prioritize variants within the terminal interface (Figure 4). Bioinformaticians also displayed the largest diversity in terms of what is desired about each variant (examples discussed in Supplementary S7). The diversity in which bioinformaticians interact with WES/WGS data likely explains why they preferred to work with a command-line rather than to be limited to a graphical tool where the functionalities are by nature more constrained and less flexible to be tailored to context-specific needs.

In contrast, clinical geneticists preferred a graphical user interface that is highly dynamic and user-interactive (Figure 5). Microsoft Excel spreadsheets were the prevalent choice of clinical geneticists and genetic counselors for viewing variant lists, despite acknowledging it as not being optimized for the purpose.

"The problem with Excel is it starts crashing when I try to feed in more than 65,000 rows of mutation, and that's just with an exome." [Clinical geneticist 01]

B. Gene-level prioritization:

This section discusses the desired prioritization strategies and executions for clinical exomes at the genic level (rather than variant level).

All user groups emphasized a desire for informatics algorithms that conduct automated literature mining or pathway analysis (the overview of such algorithms are introduced in Supplementary S8).

Figure 4: A graphical representation of the key features desired by bioinformaticians when visualizing/filtering variant sets. (**A**) Analyzing variants within a terminal environment by informaticians allows manipulation of the variant files via custom scripts and/or external command-line programs. (**B**) Variants are preferred to be visualized within a genome browser (e.g., University of California, Santa Cruz (UCSC) Genome Browser[73]) where genomic neighborhood landmarks and any additional relevant biological information (e.g., SNPs, conservation) can be displayed alongside.

The core difference between the user groups is that bioinformaticians wanted such analysis to be integrated with the rest of their command-line based pipeline, while noncomputational users wished this functionality to be accessed graphically (Figure 6).

Clinicians emphasized that while there are tools that offer online software applications to obtain candidate genes based upon keyword queries (e.g., MeSHOP,[34] Genie,[35] Ingenuity [http://www.ingenuity.com]), these capabilities are not consistently accessible to integrated WES/WGS analysis software and the output cannot be combined with exome data without additional manipulation. Expanding beyond keywords as input, clinicians further requested graphical search functionalities. One such request is the ability to filter by organ system visually where the user can click on the organ/system of interest in an anatomy diagram (Figure 6). Finally, the clinicians expressed frustration that many gene-ranking software failed to provide the primary literature when returning the results (or it was difficult to retrieve that literature).

> *"When the program predicts this gene to be related to this particular disease, I want to know how accurate it is. And not just from some kind of confidence score, but I want to see the primary literature. For instance, if the strength of association is based on GWAS literature, then I'm probably not going to treat it seriously." [Clinical geneticist 08]*

4. Data sharing with collaborators and patients

A key bottleneck to routine clinical exome analysis was identified to be the preparation of clinical reports for inclusion in medical records and delivery to other physicians. Reports should be concise and automated as much as possible including only clinical information that can be directly extracted from exome data or external databases. Figure 7 illustrates an example report separating the clinical genetic findings from technical summaries. Additionally, to streamline exchanges with patients, clinicians wanted the ability to flag genes that have been disclosed by the patients as a set they do not need to be notified about.

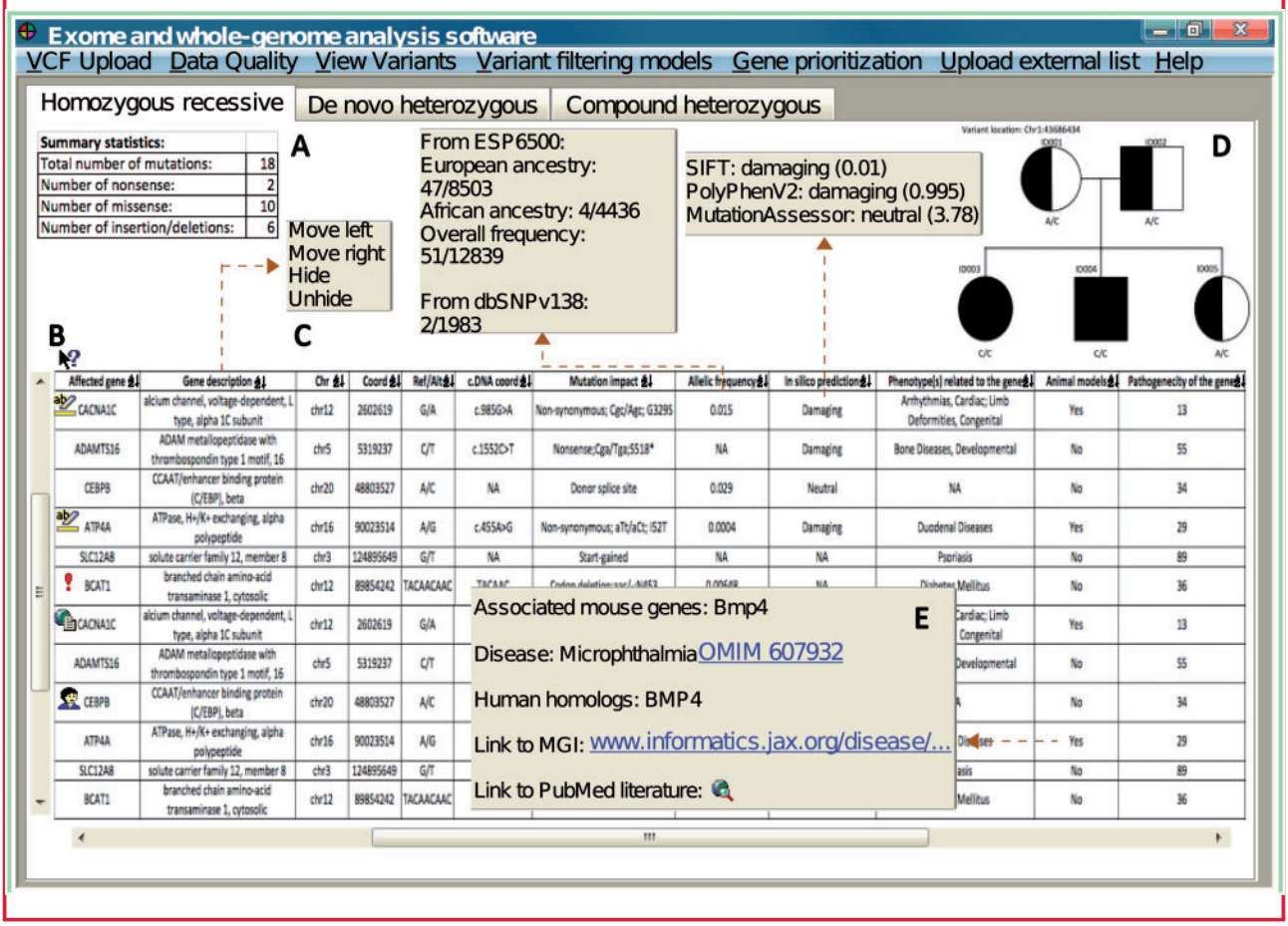
DISCUSSION

Next-generation WES/WGS sequencing is revolutionizing the study of genetic disorders, with considerable potential for successful application in clinical practice. With large-scale sequencing projects like ClinSeq[36] and Exome Aggregation Consortium (http://exac.broadinstitute.org), and collaborative efforts of sequencing consortiums (e.g., Global Alliance for Genomics and Health, http://genomicsandhealth.org) under way, the global community is in the midst of a multi-year process that will ultimately transition WES/WGS from research labs to clinical labs.[37–39] Despite the continuous flow of new software to assist in the translation process, WES/WGS analysis software for clinical genetic diagnosis is not yet in widespread use.[5,40] As bioinformaticians have been key processors of WES/WGS sequences in the research setting, they are starting to migrate into emerging clinical laboratory roles. The nature of an interdisciplinary healthcare team necessitates that the software systems and interfaces accommodate the greater diversity of participants to ensure the usability of health information and to provide the requisite utility to diverse clinical users.[41,42]

This report initiates the comparative study of cognitive patterns between healthcare professionals that closely interact with genomic data from multiple domains. Excluding the general physicians included in this study as a control group, the specialist groups represent the three classes of healthcare professionals that currently most closely interact with patient genomic data at the clinical level. While previous focus groups have studied preferences within a general population for results delivery from WES/WGS,[43,44] in this study, we interviewed bioinformaticians, clinical geneticists, genetic counselors, and general physicians to study how domain knowledge influences the cognitive patterns for the analysis of WES/WGS data, and the consequent meaning for software design.

Through a series of scenario-driven focus groups, we found that despite a common goal, the discovery of a causal candidate variant/gene, the user groups exhibit clear differences, and divergent patterns among user behaviors. Table 1 summarizes and distinguishes the software requirements from each user group.

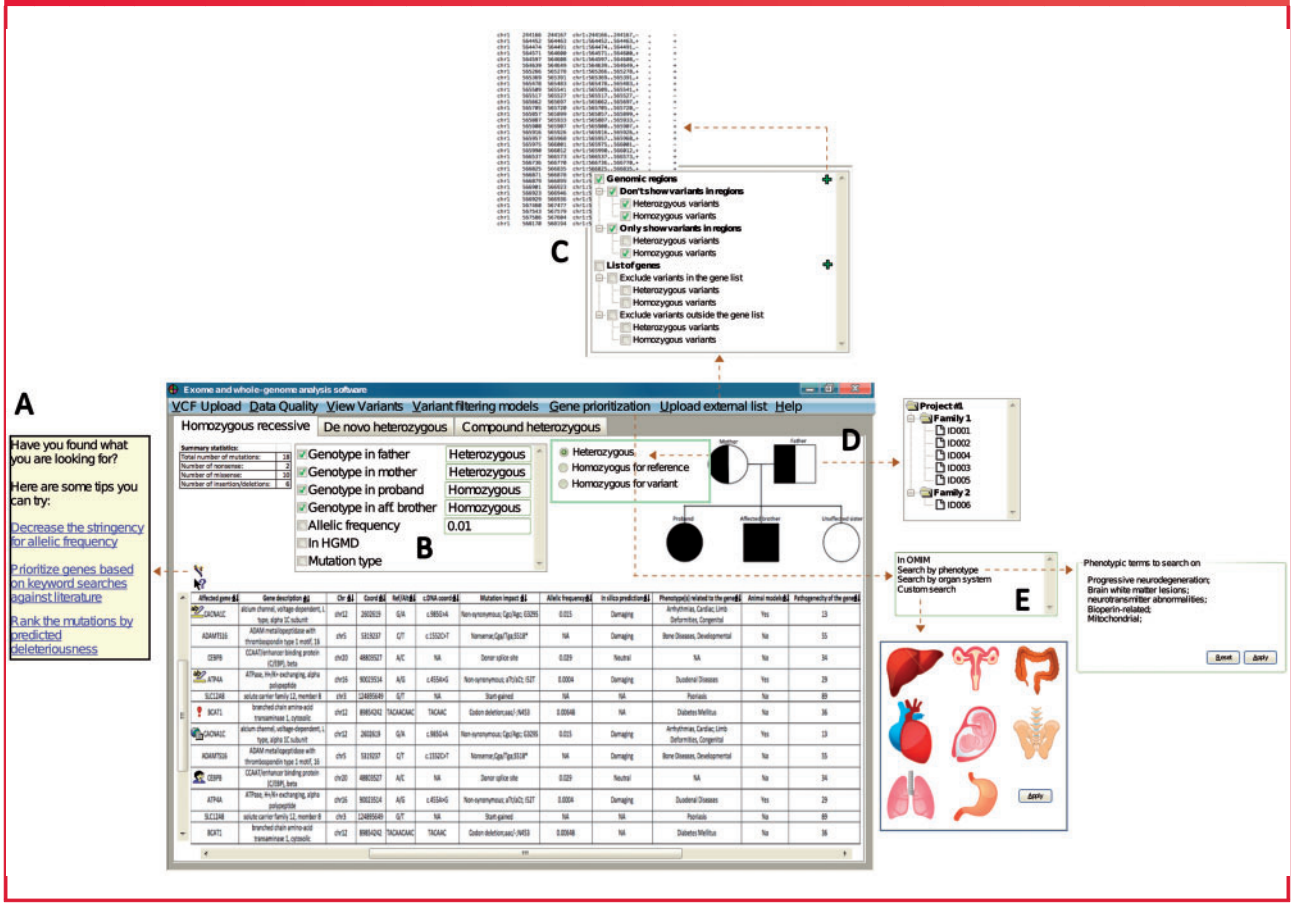
Figure 5: A graphical representation of the key features desired by clinical geneticists when performing variant visualization/analysis. Brown dotted arrows point to additional information from specific columns that is available when clicked upon. For instance, clicking the "mutation impact" column would reveal different impact predictions by mainstream prediction software and shows the level of congruency across multiple algorithms. (**A**) Classical Mendelian models should be built into the system with tabulated summaries automatically available. Outputs from each Mendelian model should be available under separate layouts (e.g., navigated by tabs). (**B**) Software should provide a quick explanation about the information contained within each column and how to interpret it. (**C**) The variant table needs to be ranked by evidence (e.g., clinically interesting variants appear at the top of the list). Variants with obvious pathogenic associations need to be automatically highlighted (e.g., flashing red notice). Aside from automated cues, clinical users wanted capabilities to highlight variants that were perceived to be of high interest, to store personal comments for specific variants (e.g., update if a variant is confirmed by Sanger sequencing), or to upload a scientific article related to a particular gene. (**D**) An integrated pedigree to visualize how the variants are segregated across a given set of related exomes, and automatically update the genotypes as users browse across different variants. (**E**) Hyperlinks that link to external databases should be discouraged. Geneticists complained that the current state of the software relies too much on external references where cross-referencing between different resources on separate interfaces is very distracting. Instead, key clinically relevant information (e.g., the phenotype of a gene knock-out experiment from animal model column) should be computationally compiled and presented within one interface, and only the technical details (e.g., how the experiment was performed) are directed to external sites.



It is our interpretation that no single interface will adequately address the needs of all users, necessitating the capacity of future WES/WGS systems to provide interface options to best meet the needs and expectations of the diverse users. The existing academic and commercial software (Supplementary S1) places emphasis upon graphical user interface that are viewed by bioinformaticians as too rigid and not customizable for distributed network analysis. While some tools may be designed to create user-friendly workflows, the lack of design-focus on clinical target users (i.e., geneticists and genetic counselors) impedes their adoption in clinical settings (Supplementary S1). The importance of user-centric themes is consistent with emerging models of care and medical decision-making support systems, such as observed for breast cancer diagnosis and management,[45,46] early recognition of sepsis,[47] antibiotics prescriptions,[48,49] and interpretation of medical images[50,51] where extensive evaluations on physicians' and nurses' interactions in work practices reveal similar concepts surrounding issues of sharing information across collaborative settings, and tensions between integration and standardization.

Given the complexities involved, software which attempts to address all possible tasks that arise in clinical genomics is less likely to be incorporated into practice than software specific to exome/whole-genome analytical tasks. To be successful, a medical decision support

Figure 6: A graphical representation of the key features desired by clinical geneticists for genetic and genic prioritizations. (**A**) When the user fails to identify any variants of clinical interest, software should provide recommendations on alternative strategies based on what the user has already explored. (**B**) The software should provide easy tracking of the filters currently applied and allow quick adjustments (in this case, via checkboxes to turn a filter on/off). (**C**) Software should allow incorporation of external files containing either genomic coordinates or list of genes to filter against variant set. (**D**) Software with an embedded dynamic pedigree would allow clinicians to graphically upload multiple exomes (e.g., trio) and assign family memberships via the pedigree. Custom inheritance models could also be setup via the pedigree by specifying expected genotype in a given model. (**E**) Ability to import free-text clinical descriptors, or access terms from a defined ontology (e.g., Human Phenotype Ontology) against which to filter for genes/variants that relate to the specified descriptions. Alternatively, a novel feature emerging from focus groups was the ability to prioritize based on organ systems.

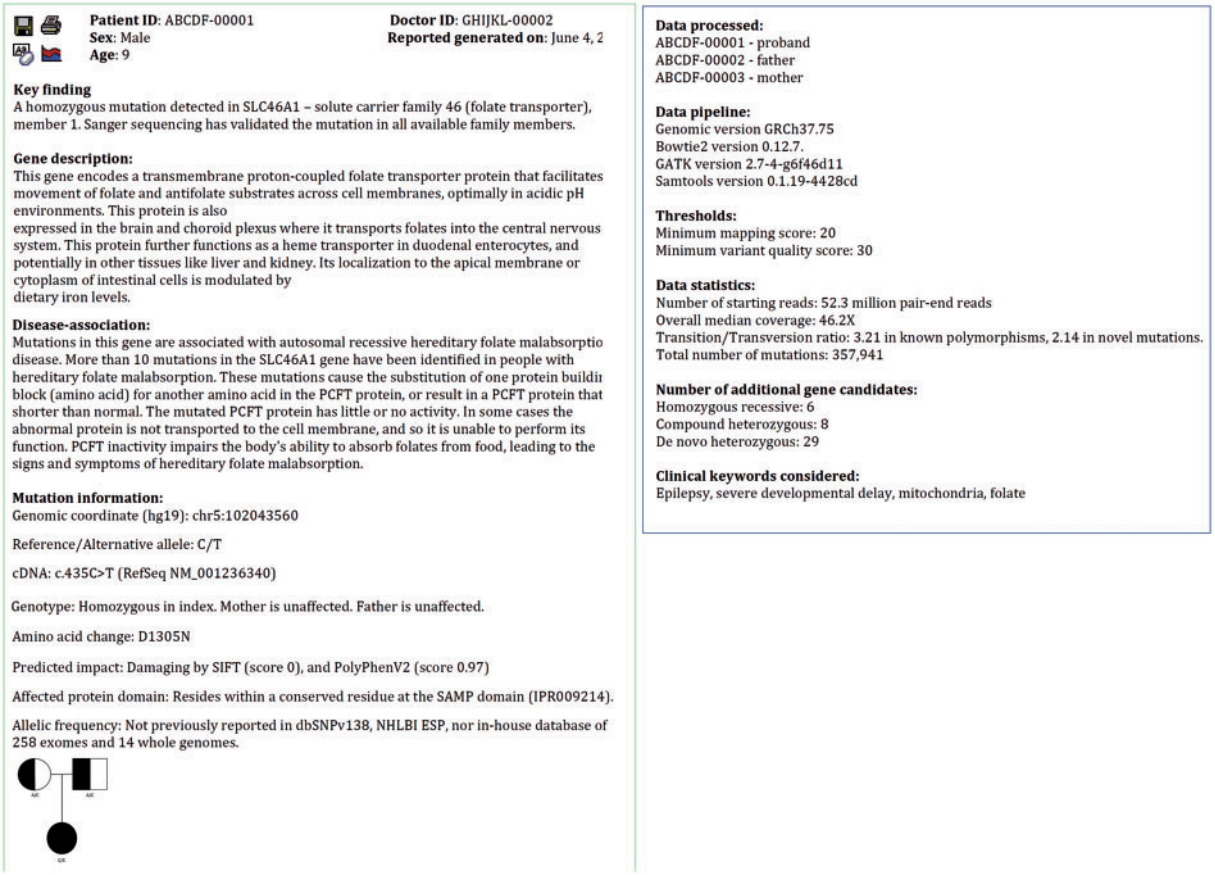


system should be compatible to an existing clinical workflow,[52,53] and actionable outputs intelligently filtered and presented at appropriate times.[54,55] In WES/WGS, we found this workflow scope includes a system's capacity to incorporate clinical keywords and genetic hypotheses pertinent to each unique patient (also cited in Luo and Liang 2014[56] and Masino et al. 2014[57]), and results delivered at specific workflow stages with respect to the disparate foci of counselors, physicians, geneticists, and bioinformaticians (e.g., Figure 1). Clinical geneticists expressed desire for an encompassing graphical design that gives them more control over the technical aspects of the pipeline, integrating genomic information with patient history but at the same time removes them from the realm of scripting and the command-line. Meanwhile, genetic counselors (and general physicians) wished to solely focus on gene prioritization and efficient delivery of final results without distraction by functionalities irrelevant to their work processes. The results highlight a need for systems to facilitate the generation of clinical reports, including the appropriate distribution of technical vs clinical details, sharing of notes between clinical staff about specific variants, overview of genes not covered by WES, and the family structure. The format of the prioritized report (Figure 7) mirrors the precedent of prioritized information in other modes of clinical reports, e.g., a radiologist's X-ray report separating clinical impressions from descriptive details of radiographic appearance of specific organs.[58]

Strong community observations should be noted by system developers. Our study confirms that an ultimate clinical WES/WGS systems will need to be well connected to online resources, such as animal model phenotypes,[59,60] biological system annotations,[61,62] and disease-focused databases.[63–65] This is concordant with earlier work that demonstrated the importance of rich access to external resources and databases.[19,66,67] The integration of metadata and diverse biological annotations to patient electronic health records will require strict compliance to standards (examples discussed in Supplementary S11). Our study further highlighted the need to integrate access within a single system, sparing users from mastering diverse interfaces.

Our results suggest future software should provide separate interfaces for each target user group. One can envision "purpose-driven" interface options, allowing users to focus on the aspect of the analysis and interpretation relevant to their duties. While the tailored software

Figure 7: An example of automated clinical reporting summarizing the clinical findings from WES/WGS. (**A**) The system should allow clinicians to save, edit text, and insert custom images to the report. The report is designed to be a skeleton for clinicians to build on. (**B**) Key genetic findings related to the clinical phenotype should be stated right on the front page. These include known clinical relevance about the mutated gene (e.g., what is the biological role of the gene, what phenotype does a person exhibit when the gene is mutated) (**C**), the type and nature of the mutation (e.g., what is the genomic and transcript coordinate of the mutation, what type of mutation is it, has the mutation been previously reported in clinical literature, what is the allelic frequency, and how is it transmitted across the given family) (**D** and **E**) All other information not directly related to the key finding (e.g., the thresholds used by the bioinformatics pipeline that generated the dataset) should be discussed in subsequent pages.



Patient ID: ABCDF-00001
Sex: Male
Age: 9

Doctor ID: GHIJKL-00002
Reported generated on: June 4, 2

Key finding
A homozygous mutation detected in SLC46A1 – solute carrier family 46 (folate transporter), member 1. Sanger sequencing has validated the mutation in all available family members.

Gene description:
This gene encodes a transmembrane proton-coupled folate transporter protein that facilitates movement of folate and antifolate substrates across cell membranes, optimally in acidic pH environments. This protein is also
expressed in the brain and choroid plexus where it transports folates into the central nervous system. This protein further functions as a heme transporter in duodenal enterocytes, and potentially in other tissues like liver and kidney. Its localization to the apical membrane or cytoplasm of intestinal cells is modulated by
dietary iron levels.

Disease-association:
Mutations in this gene are associated with autosomal recessive hereditary folate malabsorptio disease. More than 10 mutations in the SLC46A1 gene have been identified in people with hereditary folate malabsorption. These mutations cause the substitution of one protein buildi block (amino acid) for another amino acid in the PCFT protein, or result in a PCFT protein that shorter than normal. The mutated PCFT protein has little or no activity. In some cases the abnormal protein is not transported to the cell membrane, and so it is unable to perform its function. PCFT inactivity impairs the body's ability to absorb folates from food, leading to the signs and symptoms of hereditary folate malabsorption.

Mutation information:
Genomic coordinate (hg19): chr5:102043560

Reference/Alternative allele: C/T

cDNA: c.435C>T (RefSeq NM_001236340)

Genotype: Homozygous in index. Mother is unaffected. Father is unaffected.

Amino acid change: D1305N

Predicted impact: Damaging by SIFT (score 0), and PolyPhenV2 (score 0.97)

Affected protein domain: Resides within a conserved residue at the SAMP domain (IPR009214).

Allelic frequency: Not previously reported in dbSNPv138, NHLBI ESP, nor in-house database of 258 exomes and 14 whole genomes.

Data processed:
ABCDF-00001 - proband
ABCDF-00002 - father
ABCDF-00003 - mother

Data pipeline:
Genomic version GRCh37.75
Bowtie2 version 0.12.7.
GATK version 2.7-4-g6f46d11
Samtools version 0.1.19-4428cd

Thresholds:
Minimum mapping score: 20
Minimum variant quality score: 30

Data statistics:
Number of starting reads: 52.3 million pair-end reads
Overall median coverage: 46.2X
Transition/Transversion ratio: 3.21 in known polymorphisms, 2.14 in novel mutations.
Total number of mutations: 357,941

Number of additional gene candidates:
Homozygous recessive: 6
Compound heterozygous: 8
De novo heterozygous: 29

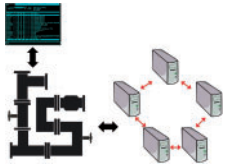
Clinical keywords considered:
Epilepsy, severe developmental delay, mitochondria, folate

is fitted to individual domains, it must at the same time facilitate collaboration, as increasingly diverse expertise is key requirement for WES/WGS interpretation. The informatics specialists may be charged with reporting on data linking candidate genes to specific biological processes, clinical geneticists will evaluate specific mutations for a causal role in disease/phenotype, and genetic counselors will indicate the variations that need to be conveyed. These activities are interactive and may require cycles of expert attention. Insights to overcome socio-technical challenges can be drawn from research in Computer-Supported Cooperative Work,[68] including themes surrounding information credibility,[69] coping with narrative and numeric data,[70] scalable methods for managing increasingly large datasets,[71] and caution surrounding interpretation of automated systems[72] (discussed further in Supplementary S10). As WES/WGS analysis software matures, it will empower clinicians with more automated procedures, which we anticipate will decrease dependency on bioinformaticians for data processing. These experts will continue to be closely involved, developing and applying new approaches for the discovery and interpretation of additional genetic alterations. Advances over the coming years will result in new requirements for collaborative interactions, for instance, as the current focus on alterations in protein coding sequences expands to include regulatory sequence alterations. Expansion of the cooperative capacity of the software will assist the diverse users as the field matures.

CONCLUSIONS

As high-throughput WES/WGS technologies continue to mature, healthcare providers need efficient software to facilitate interpretation for clinical decision-making. By conducting multiple focus groups of diverse healthcare classes active in clinical genetics, our present study reveals there are distinct types of WES/WGS analysis needs for different classes of domain specialists. The results presented illustrate the cognitive processes and tentative designs envisioned by the range of clinical professionals key to the process. A natural follow-up for future work is to implement the features into a prototype software package and conduct intervention trials to evaluate effectiveness and performance within clinic sites.

Table 1: An overall summary of the desired software features and design architectures across bioinformaticians, clinical geneticists, genetic counselors, and physicians.

	Properties for analytical interface	Properties for reporting interface	Multidisciplinary collaboration
Bioinformaticians 	• Prefer terminal-based interfaces due to superior flexibility for customizing analyses, and compatibility with distributed computing for data processing. 	• Desire a digital synchronous collaborative environment for multidisciplinary team interactions. 	• Suggest new software capacity to foster collaborations with geneticists and counsellors, including secure method of sharing genomic information and personal annotations. • Suggest a focus on visually friendly representations of complex data to inform clinical users.
Clinical geneticists 	• Desire capacity to participate in data processing. • Prefer a graphical user interface for navigation and execution. • Seek support for incorporation of patient phenotype via clinical text-mining and links to biological databases for gene–disease associations. • Desire a visually dynamic way to explore the genomic dataset, across varying statistical thresholds.	• Desire intelligent system that will automatically highlight abnormal data qualities and/or clinically relevant information (e.g., *in silico* prediction of clinically relevant variants). • Prefer a system that consolidates key information from diverse resources into one interface, rather than distributing across multiple panels.	• Necessitates software that connects to collaborative networks to discover similarities of patient cases within institutions and globally. 
Genetic counsellors and general physicians 	• Prefer a streamlined, simple interface related strictly to their domain. Graphical interface should exclude functionalities not related to variant/gene-level prioritization.	• Benefit from automated generation of clinical report that prioritizes the clinically relevant variants and masks the clinically uncertain results.	• Achieve better workflow efficiency when software maintains an environment to collaboratively review and annotate the variant data with clinical geneticists and bioinformaticians.

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LIMITATIONS

The limitations to this study are discussed in Supplementary S12.

CONTRIBUTORS

C.S., A.K., and W.W.W. designed the study. C.S. carried out the experiment and data analysis. A.K. and W.W.W. assisted with the data analysis. C.V.K. assisted with the experiment setup. C.S. wrote the manuscript. All authors read, edited, and approved the final manuscript.

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COMPETING INTERESTS

The authors have no competing interests to declare.

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SUPPLEMENTARY MATERIAL

Supplementary material is available online at http://jamia.oxfordjournals.org/.

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