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ABSTRACT

Objectives There is a need in clinical genomics for systems that assist in clinical diagnosis, analysis of genomic information and periodic reanalysis of results, and can use information from the electronic health record to do so. Such systems should be built using the concepts of human-centred design, fit within clinical workflows and provide solutions to priority problems.

Methods We adapted a commercially available diagnostic decision support system (DDSS) to use extracted findings from a patient record and combine them with genomic variant information in the DDSS interface. Three representative patient cases were created in a simulated clinical environment for user testing. A semistructured interview guide was created to illuminate factors relevant to human factors in CDS design and organisational implementation.

Results Six individuals completed the user testing process. Tester responses were positive and noted good fit with real-world clinical genetics workflow. Technical issues related to interface, interaction and design were minor and fixable. Testers suggested solving issues related to terminology and usability through training and infobuttons. Time savings was estimated at 30%–50% and additional uses such as in-house clinical variant analysis were suggested for increase fit with workflow and to further address priority problems.

Conclusion This study provides preliminary evidence for usability, workflow fit, acceptability and implementation potential of a modified DDSS that includes machine-assisted chart review. Continued development and testing using principles from human-centred design and implementation science are necessary to improve technical functionality and acceptability for multiple stakeholders and organisational implementation potential to improve the genomic diagnosis process.

Summary

What is already known?

- There is a need in clinical genomics for tools that assist in analysis of genomic information and can do so using information from the electronic health record.
- Such tools should be easy to use, fit within clinical workflows, and provide solutions to priority problems as defined by clinician end-users.
- Natural language processing (NLP) is a useful tool to read patient records and extract findings.

What does this paper add?

- We demonstrated the use of Human-centred design and implementation science principles in a simulated environment for assessment of a new version of a decision support tool prior to large-scale implementation.
- This study provides preliminary evidence that a clinical decision support tool with machine-assisted chart review is acceptable to clinical end-users, fits within the clinical workflow, and addresses perceived needs within the differential diagnosis process across all Mendelian genetic disorders.
- Terminology codes for diagnostic decision support systems should have levels of granularity tuned to the sensitivity and specificity appropriate to its various functions, for example, NLP versus chart documentation.

INTRODUCTION

Clinical decision support (CDS) integrated into electronic health records (EHRs) has long been considered a promising way to improve patient outcomes and decrease inefficiencies.[1–4] It is also recognised that CDS must be designed with the user in mind, fitting the concepts of human-centred design with computer interfaces at the individual clinician level.[1 5] Design alone, however, is insufficient to facilitate implementation. For CDS to impact care and patient outcomes, it must fit within clinician workflow and provide a solution to a priority problem for the clinician and the healthcare system.[4 6–8]

Diagnostic decision support systems (DDSSs) are a key type of CDS needed in genomics to supplement a shortage of

trained clinicians and address the inherent complexity of genomic diagnosis.[9 10] This complexity arises from the heterogeneous nature of genetic diseases, the variable expression in patients and the degree of overlap in findings (ie, signs, symptoms and test results) among genetic conditions, sometimes differentiated only by onset age of individual findings.[11] Position statements and a systematic review note two new functions needed for DDSSs in genomics: (1) a cost-effective, regular approach to re-evaluation of patient cases in light of new findings or genetic knowledge, when testing does not immediately yield a diagnosis; and (2) developing machine-assisted chart review.[12 13] Most genomic patient records are extensive with input from by multiple clinicians, such that manual review is prohibitively time-consuming; resulting in added costs from repeated or unnecessary tests and increased risk of missed information that could have facilitated timely diagnosis. Because most of the relevant information is in unstructured clinical notes, approaches such as natural language processing (NLP) are needed to automate and assist this manual process.

To address both re-evaluation and automation, we adapted a commercially available DDSS already capable of incorporating genomic sequencing data to perform automated chart review and present the information to a clinician in the form of findings obtained through structured data mining and NLP of an EHR. We then created clinical case vignettes to simulate the real-world clinical diagnostic workflow for user testing. The goal was to provide preliminary evidence of usability, perceived fit with clinical need and workflow, and potential for implementation into the real-world clinical environment.

METHODS

Setting

Development of the clinical case vignettes, simulated EHR environment, and user testing were conducted at Geisinger, a healthcare system in rural Pennsylvania.

Adapting a DDSS for machine-assisted chart review of clinical findings

We adapted SimulConsult's Genome-Phenome Analyzer, as it is the one DDSS that allows for detailed analysis of clinical information, including pertinent negatives, findings onset information and frequency and treatability of diseases. It has also been shown to be accurate and helpful in clinical diagnosis, including interpreting genomic results.[14–16] Described in detail elsewhere,[11 14 15] SimulConsult correlates annotated variant call files (VCFs) with patient-specific clinical and family history information; and the underlying algorithms include age-dependent Bayesian pattern-matching and computational metrics of usefulness and pertinence. SimulConsult also generates a Patient Summary for saving interim patient findings and a customisable genomic return of results (RoR) report shown in previous research to be effective for facilitating standardised communication for patients and referring clinicians.[17–20] When clinicians enter findings, the DDSS returns a ranked list of candidate diseases and suggestions of other findings to check, ranked by usefulness in narrowing the differential diagnosis in a way that accounts for cost and treatability; thus facilitating the iterative approach of information gathering in diagnosis.[21 22] For each finding, th presence (with onset age) or absence can be specified (figure 1).

We used the Logica platform to create a simulated EHR and the cTAKES tool with the Unified Medical Language

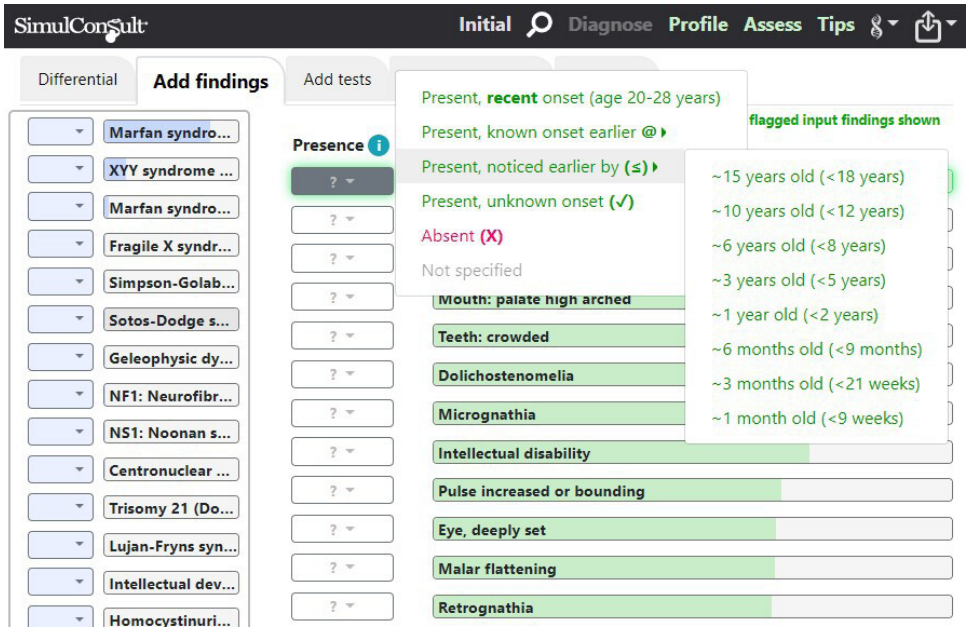

Figure 1 SimulConsult main interface showing ranked list of candidate diseases and guidance for entering finding presence (or absence) with onset age.

Table 1 Adaptations made to existing DDSS to create GPACSS

Adaptation	Component	Approach
Overall design	SMART-on-FHIR enabled EHR	► Logica platform (https://www.logicahalth.org/; formerly Health Services Platform Consortium)
	Archive	► Custom archive stores key files ► RESTful interface.
Coordination and communication	User interface	► SMART-on-FHIR application (GPACSS FHIR app client, figure 2). ► Interface allows user access to DDSS directly from patient record. ► Choice to launch with no findings or with findings previously saved.
	Coordination	► GPACSS 'Coordinator' application programming interface (API) saves the NLP output ► Matching of UMLS codes in NLP output to DDSS findings ► Send the matched flagged findings to the DDSS at launch (figure 2)
Natural language processing	Extraction of findings	► NLP: open source Apache cTAKES V.4.0.[23] ► cTAKES default modules to handle sentence boundary detection, tokenisation, normalisation, tagging parts of speech, recognising named entities and negation. ► cTAKES pretrained module to recognise UMLS concepts in text.
	Mapping in DDSS	► DDSS findings mapped within the DDSS to one or more UMLS and Human Phenotype Ontology codes. ► Mapping strategy minimises false negatives in term capture while tolerating false positives (identifying information unrelated or irrelevant to the diagnostic process).
	Display in DDSS	► Findings identified by NLP display a flag icon. ► Clicking the flag enables viewing of metadata.

DDSS, diagnostic decision support system; EHR, electronic health record; GPACSS, Genotype-Phenotype Archiving and Communication System with SimulConsult; UMLS, Unified Medical Language System.

System (UMLS) module[23] for NLP of patient notes. Steps in adaption included (1) mapping DDSS findings to Human Phenotype Ontology (HPO) and UMLS codes, including creation of hundreds of new HPO terms resulting in creation of new UMLS concepts, (2) using results from NLP analysis of EHR notes to flag 'Mentions' of the findings used by the DDSS and (3) augmenting the DDSS's interface to present the flagged findings with contextual information needed to clinically assess the information (table 1).

The architecture of the resulting prototype, called the Genotype-Phenotype Archiving and Communication System with SimulConsult (GPACSS), is shown in figure 2.

Clinician review of the flagged findings created from the automated findings search using NLP is facilitated through flag icons (figure 3). Through this 'machine-assisted' chart review, the clinician reviews flagged findings and decides whether and how to specify presence (with a particular onset) or absence (or omit) as shown in figure 1. The mapping of DDSS findings to multiple

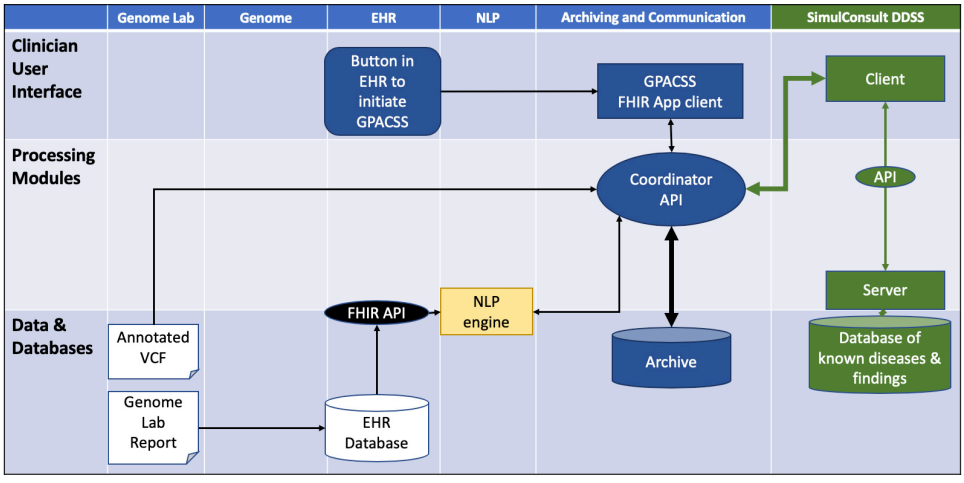

Figure 2 Architecture of the Genotype-Phenotype Archiving and Communication System with SimulConsult (GPACSS). The key components are the coordination/archiving system, the DDSS and the NLP. DDSS, diagnostic decision support system; EHR, electronic health record; NLP, natural language processing.

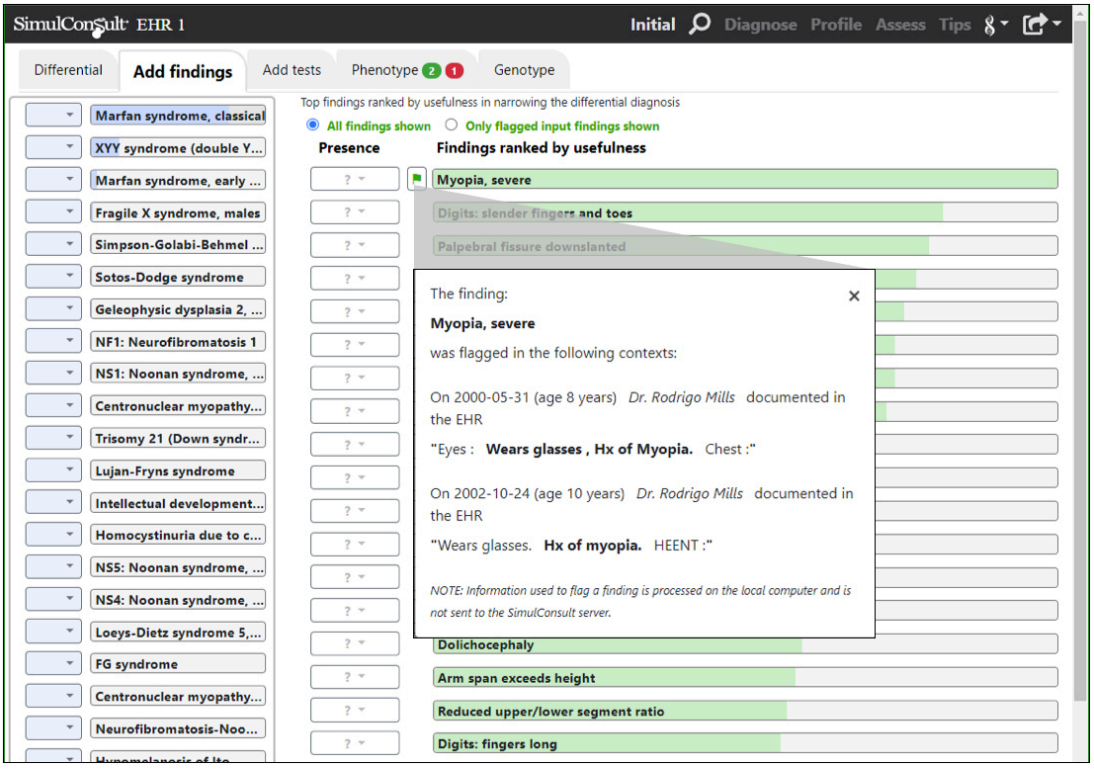

Figure 3 Flagged findings with EHR text display for DDSS. A finding having a flag icon indicates that information was found in the EHR. Clicking the flag shows the various mentions of the flagged finding. DDSS, diagnostic decision support system; EHR, electronic health record.

UMLS concepts was chosen to minimise false negatives in concept identification; relying on the user decisions about findings and the limited set of UMLS concepts to minimise false positives (table 2).

Creating simulated cases

Three cases of increasing complexity were created using real but deidentified clinical phenotypic and time course data from medical notes of Geisinger patients with known genetic diagnoses (online supplemental table 1). Cases were selected for conditions of varying complexity yet relatively common in the context of rare disease and where diagnosis might be difficult using phenotype alone. Simulated cases were created by research assistants trained in capturing information from the EHR, supervised by a practicing Geisinger clinician certified in genetics and informatics. The three final cases were reviewed by a second Geisinger physician certified in genetics and informatics prior to user testing.

Case vignettes for the test scenarios assumed that some patient characterisation was previously noted by the clinician and genomic results were now available and could be interpreted with clinical information available in the

Table 2 Solutions for mnimising false positives and negatives identified through NLP and DDSS by clinician review

False negative/positive problem	Solution included in GPACSS
Minimising false negatives on NLP flagging of findings	► Include parent and child codes (eg, finding of intellectual disability in DDSS includes codes for developmental delay and particular types of intellectual disability).
Minimising false positives through the DDSS Usefulness metric	► Use DDSS usefulness algorithm[30] to display flagged findings; thus prioritising data of greater relevance and de-prioritising data of low relevance for clinician review.
Minimising false positives through clinician verification	► Use flag icon to indicate findings identified through NLP (figure 3). ► Clinician clicks the flag icon to display information needed to assess reliability, presence or absence, and onset. ► Information displayed from the EHR includes date of chart note, observer identity and three sentences of chart note (sentence with finding plus preceding and subsequent sentence).

DDSS, diagnostic decision support system; EHR, electronic health record; GPACSS, Genotype-Phenotype Archiving and Communication System with SimulConsult; NLP, natural language processing.

EHR (online supplemental figure A). For the three cases, a total of five findings were used as initial information before the genomic results, with three (one per case) being flagged findings identified through NLP. This created a 'near live'[24] experience within the simulated EHR for user testing while limiting the expense and time of EHR integration during this preliminary phase.

User testing methods

Participants

GPACSS is both a DDSS and communication tool to facilitate utilisation of genomic and phenotypic information available in the EHR by all clinicians to improve patient care within a healthcare system. Therefore, we purposively selected primary testers from Geisinger staff representative of current end users of the genome-phenome analyzer. Because a limited number of individuals at Geisinger regularly engage in using genomic information for differential diagnosis, we followed guidance recommending 3–5 evaluators for preliminary usability testing.[25] A group of secondary testers (inclusive of a pilot tester) with other roles in the genetic testing and interpretation process were purposively selected for potential broader utilisation in the healthcare system.

Testing sessions

At the beginning of each session, testers viewed a 4 min training video (https://simulconsult.com/videogpacss) beginning from saved patient findings, then importing a VCF, and review of flagged findings to make a diagnosis and create a customisable patient-friendly RoR report.

A semistructured interview guide (online supplemental file 3) was created to elucidate factors relevant to human factors in CDS design (information, interaction, interface)[1 5 26] and organisational implementation (acceptability, perceived need, feasibility, workflow fit).[27] We used a think aloud[24] approach where testers were asked to verbalise thoughts while using the GPACSS prototype with the interviewer asking questions as needed and at key points in the testing to create a cognitive walkthrough with heuristic evaluation.[25 28] Testers were invited via direct contact from study staff and provided a description of the study. At the beginning of each session, study staff reviewed a study information sheet and obtained verbal consent to participate. Test sessions lasted 2 hours and testers received a US$100 gift card.

An experienced interviewer (AKR) and observer (MAW) from Geisinger worked with each tester to imagine using GPACSS for each test scenario. The interview and process were piloted with a cancer genetic counsellor reviewing one test vignette. At the end of the session, testers were asked a series of study-specific questions using a 0–10 rating scale (hard to easy) to rate the overall usefulness, satisfaction, and navigation. Transcripts were created from the audio portion of each session and the computer screen was video recorded to capture tester movement through GPACSS.

Analysis

Two Geisinger coders (MAW and JCR) viewed each user test session recording, read transcripts and created a codebook of themes identified across sessions. Transcripts were coded and the corresponding quotes were organised into a matrix using the three categories of CDS components (information, interface and interaction) identified by Miller *et al*,[1] and categories of acceptability, perceived need, feasibility and workflow fit according to Rogers' Diffusion of Innovations in organisations constructs.[27] Coders analysed transcripts independently and reviewed for agreement with discrepancies resolved by the primary author.

RESULTS

Three clinicians currently using genomic information to diagnose patients participated as primary testers: a paediatric geneticist (orders exomes daily), internal medicine physician (orders 4–5 exomes per month) and a paediatric genetic counsellor. Three additional clinicians participated as secondary testers; representing broader usability within the healthcare system: the pilot tester (cancer genetic counsellor), a laboratory director (conducts variant interpretation) and a laboratory genetic counsellor (conducts variant analysis).

GPACSS usability: human factors of CDS design

Overall impression of the prototype was positive. Testers raised general issues relevant to human factors in CDS design.[1 5]

Interface

Testers liked the flagged findings (figure 3), the contextual information for each mention in the EHR, and the rank ordering of flagged findings by usefulness. The visualisation of the evolving differential diagnosis and the automated RoR report for sharing with patients and referring clinicians, including the ability to save and access this report from the EHR were also appreciated.

The interface was noted to be complex, but testers stated this was expected due to the inherent complexity of genetic diagnosis and that they anticipated a learning curve to develop proficiency. Placement, positioning and the multiple presentation layers (text and graphics in the interface)[1] were well liked. In particular, the 'Assess diagnosis' display was noted as valuable because it made transparent the logic used by the DDSS in comparing patient findings to information about the disease. Of note, each tester interpreted differently the meaning of the graphical bars and shading, however, this did not hinder their ability to make the diagnosis, and the bar itself was appreciated as a design feature. To help with interpretation, more labelling was suggested (table 3).

Interaction

Testers were thoughtful and purposeful using GPACSS. Notably, in case 3 (the most complex case), one primary

Table 3 GPACSS usability: human factors of CDS design and Organisational implementation factors through tester Experiences*

Human factors of CDS design	Interface	'More training would be good… unless I was doing it all the time for all of my patients, every step, I might not realise that some of the features are available…'(Tester 3)
		'These bars are different lengths, so I assume it's having something to do with frequencies… so I'm not sure why this part is purple…if there were something [on the assess diagnosis tab] that said this is 100% over here and this is 0% over here, that would kind of help, if I knew that that was the case… I'm not sure what these other colors are referring to.'(Tester 5)
	Interaction	'To me, the green bar in it shows me they are confident that this genetic variant aligns with the phenotypic markers that we have identified. I don't necessarily know how far the bars will tell me they're confidence in pathogenic vs VUS.'(Tester 3)
		'It's going to take a lot to learn. A lot of clicking back and forth and it's not super intuitive but I get it. So, the report gets generated and that becomes part of the record. I can see how that can be helpful because it has now particular phenotypical diagnosis and even genetic finding'(Tester 2)
	Information	'The term pertinent gene zygosity is not something I would normally make part of my lexicon…I have a general sense of the term zygosity but I can't remember the last ten years using that term in any of my discussions in clinical care or genetics in some of the cases I found what's their zygosity' (Tester 2)
		'But the variant severity score doesn't mean anything to me personally. To me it's easier to know, if you verify know the true classification they are giving it… Pathogenic, likely pathogenic VUS benign.' (Tester 3)
		'I think this one is nice [the 'Mention' displayed in a flagged finding]. Whenever someone says it had been noticed earlier by, it's nice when someone is talking about their niece or nephew, or like a proband cousin, they are saying they had myopia and I remember them having glasses before they were 5 years old.' (Tester 3)
Organisational Implementation Factors	Acceptability	'I would use it most of the time. To me, this is the frontier of genomic medicine and I look at my role as not only taking care of a patient but figuring out how we make genomics part of everyday medical practice. The useful things in the chart, genetics people can now get to right away'.(Tester 2)
		'…Typing them up, writing the summary [of all the patient findings in the chart]. If I could see what's been flagged in the chart, see what has not actively been flagged and decide do I need to go back and look at it or not. It would save my time' (Tester 3)
		'I think the interface is really good, in that you have that ability to explore those variants that may or may not make it on the reports that we get now, so you can drill deeper if you want. (Tester 5)
	Perceived Need	'…The report is a great idea for highlighting why you think it's [the care instructions] important, [in] a standard format… The average primary care physician that gets the genetic testing reports, says I don't know what this means at all. I think this [the Prognosis Table] is a step towards making it more understandable.' (Tester 2)
		'Everything's there [in the chart] and the question is how easy is it to find. I'm sure if you're a malpractice lawyer you get very good at pulling stuff out of these charts and asking why didn't you see that. Yet I can't look at everything.' (Tester 2)
		'This is stuff that you are doing anyway… you could make your note a lot shorter and just refer to that document [the automated Summary] … I like the idea that you can explore. Clinical genetics now is limited on time.' (Tester 5)
	Workflow Fit	'It's nice because it helps guide me… it's very easier for me to realize that Prader–Willi is associated with narcolepsy…'(Tester 3)
		'I think the nice part is I don't have to go searching myself to find all the signs and symptoms associated with it and potentially miss something, that I may not know is a less common finding or feature of the condition. That actually could be beneficial for a provider or for us to give to the testing lab, to say these are all symptoms that we see, and then analyzing the data' (Tester 3)

*Comments from primary user-testers only (testers experienced with differential diagnosis of genetic conditions through sequencing): n=3; paediatric genetic counsellor, paediatric geneticist, internist ordering 4–5 exomes in the past month.
CDS, clinical decision support; GPACSS, Genotype-Phenotype Archiving and Communication System with SimulConsult.

tester did not immediately choose the top diagnosis offered by GPACSS. Supported by the data displayed, the tester indicated that to make a definitive diagnosis they would next evaluate for the second-ranked disease—as that condition had a test that was easy and accurate and the condition was also more treatable—indicating utilisation of the DDSS as intended and consistent with clinical diagnostic decision making.

Testers initially expressed concern around 'too many clicks' and 'click fatigue' but noted as they progressed through the cases that the clicking was unavoidable and necessary. For example, they saw value in taking the time to correctly specify onset information (which requires clicking and cognitive load in the DDSS), as this is part of the genetic diagnostic process. 'Cognitive Load' in DDSS testing refers to additional thinking required to interact with the tool, and the general recommendation is to minimise this in CDS design.[1] Testers who commented on the cognitive load required to review flagged findings and choose age of onset noted the cognitive load as similar to completing this task without GPACSS.

Information

Testers appreciated resources such as the hover feature that revealed synonyms to findings and requested even more hovers and infobuttons. Confusion over some terminology occurred, notably 'zygosity' and 'severity score,' when reviewing the genomic variants; as only some testers located the explanatory resource for these terms.

The fact that the EHR 'Mentions' displayed in flagged findings were sometimes triggered by parent or by child concepts was noticed by all testers, and some stated the findings used in the DDSS were not as granular as they were expecting. Regardless, testers recognised and emphasised the importance of being able to review the 'Mention' information from the EHR and manually adjust for any false positives and false negatives from the NLP process.

GPACSS usability: organisational implementation factors

Acceptability

For the primary testers, satisfaction averaged 8.5 out of 10 (range 8–9.5) and navigation ease averaged 8 out of 10 (range 7.5–9). All three felt GPACSS would save time throughout the clinical process, with one primary tester estimating it at 30%–50%. Specific value in time saved was noted for chart review by all testers.

Perceived need

The RoR report and detailed prognosis table[20] generated in each scenario was highly valued for being standardised and for its ability to communicate complex genetic information to patients and other clinicians (table 3). The RoR report was also noted as an improvement over current laboratory reports; with one tester stating it was 'where the most utility would be' (Tester 4).

Testers exhibited learning and familiarity with GPACSS as they progressed through the testing session; appreciating the DDSS assistance as each vignette increased in complexity; noting 'It takes it [clinical diagnosis and diagnostic thinking] to a higher level'. [Tester 2]. Primary testers expressed readiness to adopt the tool in clinical practice; and one (paediatric geneticist) suggested GPACSS could also serve as a differential diagnosis training tool for medical students and residents in their clinic.

Two secondary testers (lab director and variant analyst) expressed enthusiasm that GPACSS could fill a need for in-house sequencing laboratories because full EHR data would be available during sequence interpretation. These testers also hypothesised that the ability to periodically re-analyse an existing VCF in minutes using GPACSS would improve the diagnosis rate over time.

Workflow fit

The three primary testers noted that the GPACSS process as tested fit with their clinical workflow diagnosing genetic conditions. As an added benefit, they described how using GPACSS also helped them learn about diseases and associated findings with which they were less familiar (table 3).

The three secondary testers questioned GPACSS fit with a clinical genetic testing workflow in which only a report with variants labelled as to pathogenicity and association with a condition (implying a clinical diagnosis) is received from an external lab. However, they did identify value and possible workflow fit for situations with uncertainty as to the diagnosis after sequencing or where flagged findings and the usefulness ranking would allow clinicians to review the EHR with flagged findings in light of the genomic information to make the diagnosis.

DISCUSSION

We provide preliminary evidence through user testing in a simulated real-world clinical workflow that the combination of NLP with a CDS tool optimised to support the clinical process of differential diagnosis may address the needs of those involved in this complex task. Such assessment of fit is critical if CDS is to fulfil the promise of standardising and improving care.[1 4 5 8]

Technical issues related to the interface and interaction of CDS design were minor and fixable; as were issues with design layout. Despite initial remarks on the number of clicks and cognitive load, testers acknowledged these as necessary to the genetic diagnosis process and no different than without the DDSS. Other issues related to terminology and usability could be solved and evaluated in future usability studies through a combination of training, added infobuttons and experience using GPACSS. Some of the technical gaps noted and additions requested by testers are addressed within GPACSS, however, the 4 min training video was created to provide enough instruction only to facilitate user testing. These results, therefore, provide direction for training and ongoing reference materials for future implementation.

For CDS to be acceptable and implemented by clinicians and organisations, it must fit with the real-world workflow and must present a solution to a perceived need.[5 27] All primary testers identified ways GPACSS added such value and fit and noted ways GPACSS filled multiple needs in their diagnostic workflow. Workflow fit was highest among primary testers but opportunities for workflow fit were described by all testers. GPACSS was also noted as acceptable for implementation by all testers regardless of individual issues identified and suggestions for technical improvements.

LIMITATIONS

To facilitate user testing of GPACSS in the context of clinical workflow prior to full integration and implementation, simulations of the real-world were required. Because this study used the Logica EHR simulation, benefits or drawbacks of GPACSS in a production EHR could not be directly observed. Also, full annotations for the causal variants were not included in the variant table for the simulated patients limiting full assessment of the value of the DDSS in variant interpretation. This impacted the understanding of the 'severity score' by all testers, as the annotation information that would have been provided for a real patient was not included for the simulated cases. Finally, the generic cTAKES NLP using the UMLS concepts found only 20 of the 30 (67%) pertinent positive concepts within the test cases that a paediatric neurologist (MMS) identified manually. This was sufficient for GPACSS to generate the correct differential diagnosis for user testing, as further enrichment of the generic NLP to improve detection and avoid false positives was out of scope for this preliminary user testing.[29] Subsequent automated search for UMLS terms for flagging and addition of a separate stage of text search enrichment for terms missed by the NLP such as 'tall' improved NLP yield to 30 of 30 (100%).

This simulated EHR and user testing were a necessary first step and provide data to guide implementation of GPACSS. NLP improvements and additional beta testing within an actual EHR, in real-world clinical workflows, with real patient results and in real-world clinical workflows will be necessary to fully assess individual user-level and organisational-level facilitators and barriers to use, implementation and impact on clinical care. Such studies are currently in progress.

CONCLUSIONS

This study provides preliminary evidence for the usability, workflow fit, acceptability and implementation potential of a DDSS that includes machine-assisted chart review. Overall, responses suggest the GPACSS prototype is usable based on technical CDS and human-centred design criteria, addresses perceived clinical need, and has good fit within the real-world clinical workflow of genetic testing and diagnosis. Further development is needed to improve usability for multiple clinical stakeholders and organisational implementation.

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Contributors All authors reviewed the final manuscript for submission and contributed to the study as follows: AKR contributed to the study design, conducted user testing sessions, and led the analysis, interpretation and writing of manuscript. NAW contributed to the study design, created the simulated clinical environment and the deidentified patient records, contributed to the NLP testing and adaptation of the DDSS and manuscript revisions. TNP was the lead developer on the NLP and the integration with the SimulConsult API. CJ, TJ, TNP and JP contributed to NLP testing and creation of the simulated clinical environment and manuscript revisions. MAW contributed to project management, user testing recruitment, qualitative data analysis and interpretation and review of manuscript. JCR contributed to project management, IRB applications, NLP testing and creation of the simulated clinical environment and manuscript writing. MSW contributed to study design, simulated clinical environment, NLP testing and adaptation of the DDSS, user testing design and recruitment, data analysis, interpretation and manuscript writing. LKF contributed to project management, study design and manuscript revisions. PNR assisted in the tagging of DDSS findings with HPO codes and created the new codes when needed. MMS designed and implemented the adaptation of the clinical decision support tool to interact with the NLP, designed and implemented the strategy for HPO and UMLS coding, did the manual chart review to identify findings that should have been recognised by NLP, and contributed to the study design, and manuscript revision.

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Competing interests LKF and MMS have an ownership stake in SimulConsult. MMS is PI of the NIH-funded Small Business Innovation Research (SBIR) grant. LKF and MMS provided the DDSS software to Geisinger for this research, including themodifications to enable the NLP and flagged findings, but were not involved in the user testing evaluation and analysis.

Patient consent for publication Not required.

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Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. Data include qualitative interview transcripts which are not permitted for reuse.

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Supplemental table 1

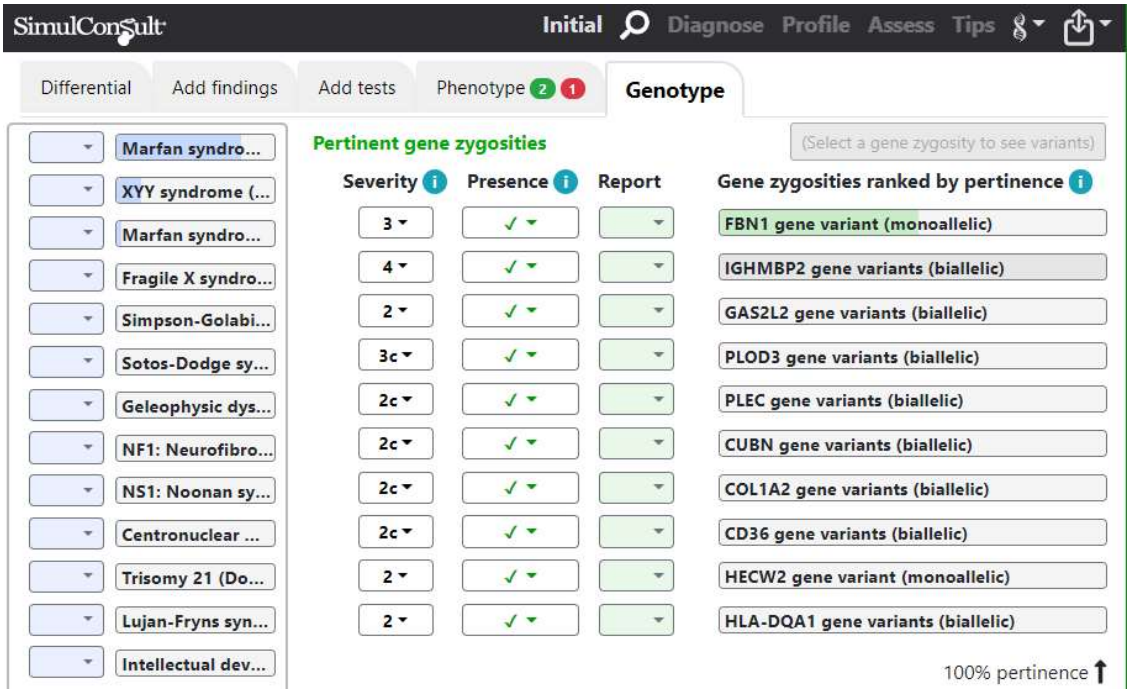
Supplemental Table 1. Creating and processing simulated patients* in GPACSS for user testing in simulated real-time clinical workflow

Simulation aspect	Process used in simulation
Phenotype	All findings discussed in the original Geisinger EHR text were retained but notes were manually rewritten by changing narrative to remove identifying information and prevent re-identification, shifting dates while maintaining chronological relationships, and shifting numeric values while maintaining appropriate range to retain clinical meaning (i.e. laboratory values for "high-abnormal" range were maintained in that value range).
Genotype	Genomic data was simulated by adding the known causal variant to variant tables generated from publicly available trios from the 1000 Genomes Project to prevent identification of a real person. However, the known causal variant was not given key annotations such as functional and conservation scores that are used in the DDSS's explanation of variant and zygosity severity scores.
Processing	Resulting simulated patient data for 3 simulated patients was loaded into the Logica platform for user testing and run through the cTAKES Clinical Pipeline using default settings.

**3 simulated patients of escalating complexity with notes and clinical findings were created based on 3 real Geisinger patients with known genetic disorders. Two others were used in earlier testing and the demo video (*https://simulconsult.com/videogpacss*).*

Supplemental figure A

SUPPLEMENTARY Figure A: SimulConsult interface showing **Gene zygosities found in the genomic analysis**



Supplemental Material - GPACSS User Testing Interview Guide

Consent/Recording:

Thank you for agreeing to participate in our testing of the Genome-Phenome Archiving and Communication System (GPACS). Our goal today is to have you simulate a clinical process for each of 3 case scenarios - going from assessment to diagnosis after genetic sequencing results. We will be recording how you use GPACS in each case, how easy/difficult it is to find what you are looking for, what works/not for you, and what your thoughts are on how helpful it is in this process. I will also be asking you to "think aloud" as you are going through this – we will be recording your thoughts and clicks, and I will be asking general and specific questions throughout.

You can stop participating at any time. At the end you will receive a gift card.

Start recording

Introduction and video instruction:

I'm going to present you with 3 clinical vignettes about cases where you might order genome/exome sequencing for the patient. After the first vignette I will show a short video that will orient you to the Genome-Phenome analyzer and how to use it to help you facilitate the diagnostic process.

I'll be asking questions as you go through each vignette, and we can watch the video again if needed.

This video will orient you to the GPACS tool as it would look in the EHR once you open with findings and start the process of reviewing the case and the genetic results. The tool finds many, but not all findings in the EHR. We will start the first vignette after you watch the video:

launch user testing orientation video

For each vignette: *Imagine you have returned the patient's chart and have opened Simulconsult with prior findings. Look around and see if you can see the findings and import the genome. Then let's do like the video and see the findings, review the chart, and create the report*

Tester process for each vignette:

1. Open with pre-loaded findings and any family history
2. Import genomic results
3. Review flagged findings and "Mentions"
4. Record pertinent negatives
5. Make diagnosis and create report

Launch GPACS Logica sandbox

Vignette 1:

You have seen a 27 year old male with pectus excavatum and tall stature. As part of your clinical process you have ordered genomic sequencing for this patient. After the genetic information is available, you return to the patient's chart to review the genetic information in light of the patient's other medical information. You launch the GPACSS system and click in as a permitted user, choose a patient, and launch SimulConsult with the prior findings already entered

Vignette 2:

You have seen a 21 year old female with seizures who sometimes has some hand wringing. As part of your clinical process you have ordered genomic sequencing for this patient. After the genetic information is available, you return to the patient's chart to review the genetic information in light of the patient's other medical information. You open an encounter and launch the GPACSS system with Your prior findings

Vignette 3:

You have seen a 14 year old female with seizures and a small head. As part of your clinical process you have ordered genomic sequencing for this patient. After the genetic information is available, you return to the patient's chart to review the genetic information in light of the patient's other medical information. You open an encounter and launch the GPACSS system with Your prior findings

Interview Questions during each case scenario (asked as appropriate in vignettes):

General question throughout: Why did you look there? Do that? Think of that? Click that? You seem to be clicking around – are you looking for something specific?

- How does the GPACSS process fit with what would normally do in this process?
    - How does GPACSS help/not?
    - What do the numbers/severity score mean to you?
    - What does the list/shading/differentials/graphics mean to you (or do for you)? **(at each screen)**
        - How do they help (or not)?
- How does GPACSS help you locate info in chart and decide whether it is relevant? How does the ordering of findings by usefulness help you focus on relevant information?
- What questions does using GPACSS bring up for you as you're using it?
    - Thoughts on the experience so far?
- What are your thoughts about the report? How would you use it? What are your questions about it?

- What would you do next in this process/case?
- Is there anything in this process you WOULDN'T use for this case? (why?)
- How did using GPACSS for this case compare with your typical process?
    - Was GPACSS intuitive?
    - What did you think about the filtering/flagging?
        - How did it make the process easier/harder?
        - What questions did you have about it as you were using it for this case?
        - Would you like more text before or after the text in bold of the mentions of a finding in the chart?
        - Would you like a hyperlink to open up the whole note in which a mention was found?
    - How difficult / easy? What needs to change?
    - Does this process fit with workflow? How/not?
- What would you do next with this case after reviewing the exome results?

CLOSING QUESTIONS:

1. How satisfied are you with whole GPACS process? (0-10 scale from "not at all" to "extremely satisfied")
    - Explain
2. How often do you think you would you use it when receiving exome results? (0-10 scale from never to always)
    - Explain
3. How confident were you with the GPACSS diagnostic support process? (0-10 scale from "not at all" to "extremely confident")
    - Explain
4. How comfortable were you with the flagged findings and chart context filters? (0-10 scale from "not at all" to "extremely comfortable")
5. How do you see yourself using this for your patients regularly?
    - What works for you to use this regularly
    - What needs changing for you to use it regularly?
6. How does GPACSS improve/not the process for you?
7. Workflow thoughts? Where to implement? What needed to implement?
8. What sort of training would you need to use this regularly?
9. Is this something you would integrate into practice? Explain.
10. How would you use it?
    - How would colleagues use it?
    - Other feedback?

DEMOGRAPHIC QUESTIONS:

1. How long have you been at Geisinger?
2. How long have you been at your current position?
3. Current department and clinical role?
4. How often do you order exomes and report results?