Clinical decision support for genetically guided personalized medicine: a systematic review

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ABSTRACT

Objective To review the literature on clinical decision support (CDS) for genetically guided personalized medicine (GPM).

Materials and Methods MEDLINE and Embase were searched from 1990 to 2011. The manuscripts included were summarized, and notable themes and trends were identified.

Results Following a screening of 3416 articles, 38 primary research articles were identified. Focal areas of research included family history-driven CDS, cancer management, and pharmacogenomics. Nine randomized controlled trials of CDS interventions for GPM were identified, seven of which reported positive results. The majority of manuscripts were published on or after 2007, with increased recent focus on genotype-driven CDS and the integration of CDS within primary clinical information systems.

Discussion Substantial research has been conducted to date on the use of CDS to enable GPM. In a previous analysis of CDS intervention trials, the automatic provision of CDS as a part of routine clinical workflow had been identified as being critical for CDS effectiveness. There was some indication that CDS for GPM could potentially be effective without the CDS being provided automatically, but we did not find conclusive evidence to support this hypothesis.

Conclusion To maximize the clinical benefits arising from ongoing discoveries in genetics and genomics, additional research and development is recommended for identifying how best to leverage CDS to bridge the gap between the promise and realization of GPM.

BACKGROUND

Genetically guided personalized medicine (GPM) entails the delivery of individually tailored medical care that leverages information about each person's unique genetic characteristics.[1] The promise of GPM has expanded as advances in genomics have accelerated over the past several decades. This promise of GPM is that research discoveries will one day lead to medical treatments and therapies that are tailored to the individual characteristics of each patient, including clinical data, genetic test results, patient preference, and family health history (FHx). GPM has the potential to increase the efficacy, quality, and value of healthcare by providing individually optimized prevention, diagnosis, and treatment.[2]

As ongoing research continues to expand the GPM knowledge base, it has become increasingly important to translate this knowledge into routine healthcare practice in order to realize the promise of GPM.[3] However, the effective realization of GPM remains very limited.[4] While this is partly due to the need for further evidence of the clinical utility and cost effectiveness of a genetically guided approach to patient care, an important additional reason is the need for information systems that assist in the translation of knowledge from bench to bedside.[5] Even without the complexity of genetics, it can often take over 15 years to translate research from bench to bedside.[6] This translational bottleneck is likely to be an even more significant problem in GPM for the following reasons.

Limited genetic proficiency of clinicians

Many clinicians receive minimal training in clinical genetics. As a result, many physicians lack the confidence and understanding needed for effectively interpreting and using genetic information in their clinical practices.[7]

Limited availability of genetics experts

Currently, there are about 3000 board-certified genetic counselors[8] and approximately 1200 medical geneticists practicing in the USA (S. R. DelBusso, American Board of Medical Genetics Administrator, October 28, 2011, personal communication). The growing utility of genetic information is putting an increasing burden on these professionals. We cannot expect these genetics experts to be readily available each time genetic information should be used to guide medical treatment. For effective, efficient, and widespread clinical use, the burden of genetic interpretation and guidance must be shared by the wider clinical community.

Breadth and growth of genetic knowledge base

There are currently over 2500 clinical genetic tests available to clinicians, encompassing a wide breadth of medical care.[9] It is therefore unreasonable to expect a clinician to remember every appropriate genetic test for a particular condition in conjunction with test-specific guidelines for ordering and interpretation. Compounding this issue, the continual growth in the knowledge base and the prospect of full genome sequencing will inevitably overwhelm clinicians' capacities to manage and leverage this information effectively for GPM unless computerized assistance is provided for interpreting and acting on this information.

Various investigators and leaders have identified health information technology as being vital to overcoming these barriers and realizing the promise of GPM.[2 10] In particular, clinical decision support (CDS) has been identified as a critical enabler of GPM.[11 12] CDS entails providing clinicians, patients, and other healthcare stakeholders with pertinent knowledge and person-specific

information, intelligently filtered or presented at appropriate times, to enhance health and healthcare.[13] CDS has the capacity to process complex, disparate data and present actionable, standardized, evidence-based recommendations in a way that is usable by a clinician in everyday practice.[11] As such, CDS can help bridge the gap between the promise and realization of GPM (figure 1). Given the criticality of CDS for realizing the promise of GPM, and given the lack of a systematic review on this topic, we sought in this paper to assess the history and state of CDS for GPM through a systematic review of the literature.

METHODS

Data sources and inclusion criteria

We searched MEDLINE and Embase from 1990 to 2011 using a search strategy adapted from previous systematic reviews of CDS,[14] genetic health services,[15] and FHx[16] (see supplementary appendix, available online only, for full search strategy). The final literature search was conducted on June 1, 2012. The inclusion criteria for the review were as follows: English article; human focus; manuscript in peer-reviewed journal; and primary focus on the use of computers to deliver genetically guided, patient-specific assessments and/or recommendations to healthcare providers and/or patients to guide clinical decision-making, as further defined in Box 1.

For all identified references, the authors reviewed titles, index terms, and available abstracts to determine if the articles appeared to meet all inclusion criteria. If insufficient information was available to make a confident decision at this stage, the article was included for full-text retrieval. Each full-text article was then reviewed to determine its final inclusion status.

Data abstraction

For each of the articles that met the inclusion criteria listed above, we abstracted data on the clinical application area, CDS type, genetic information used, primary users, article type, study location, CDS purpose, and notable informatics aspects. CDS type was defined as being either stand-alone CDS or integrated CDS. A stand-alone CDS system is a CDS system that exists in isolation from a primary clinical information system containing relevant patient data, such as an electronic health record (EHR) system. A stand-alone CDS system requires manual data input before a CDS result can be produced. In contrast, an integrated CDS system is integrated with a primary clinical information system such as an EHR system or a computerized provider order entry system to aggregate necessary patient-specific information automatically and to provide guidance within routine clinical workflows. Clinical application area was defined as the clinical domain targeted by the CDS intervention. Article type consisted of system description papers and evaluation studies of various types (eg, qualitative evaluation, randomized controlled trial). Genetic information used consisted of FHx, genotype, or both. Primary users were defined as the individuals who primarily entered information and received the results. Study location was the country or region where the research was conducted. CDS purpose identified the role of the CDS system within the context of clinical decision-making. A notable informatics aspect was also abstracted if a manuscript utilized a methodology that was considered to be of potential interest to an informatics audience. For intervention studies, additional details regarding the study size and study outcomes were abstracted.

Data analysis and presentation

Using the abstracted attributes, the manuscripts were grouped into logical categories, primarily according to CDS type and clinical application area. The findings from these manuscripts were summarized through tables and narrative discussion. In addition, notable themes and trends were identified and discussed. A quantitative analysis of CDS trials to identify features predictive of trial outcomes was considered.[14] However, due to the limited sample size of CDS trials available, such a quantitative analysis of potential success factors was not feasible.

RESULTS

The initial MEDLINE and Embase searches identified 3416 potentially relevant articles. During the title and abstract review, 82 articles were rejected for not being in English, 504 articles were rejected because they were not focused on humans, 34 articles were rejected for not being a peer-reviewed manuscript, and 2494 articles were rejected because the primary focus of the work was not on the use of computers to deliver genetically guided, patient-specific assessments and/or recommendations. The remaining 302 articles underwent full-text review, at which stage 37 articles were rejected for not being a peer-reviewed primary research article and 227 articles were rejected because the primary focus of the work was not on the use of computers

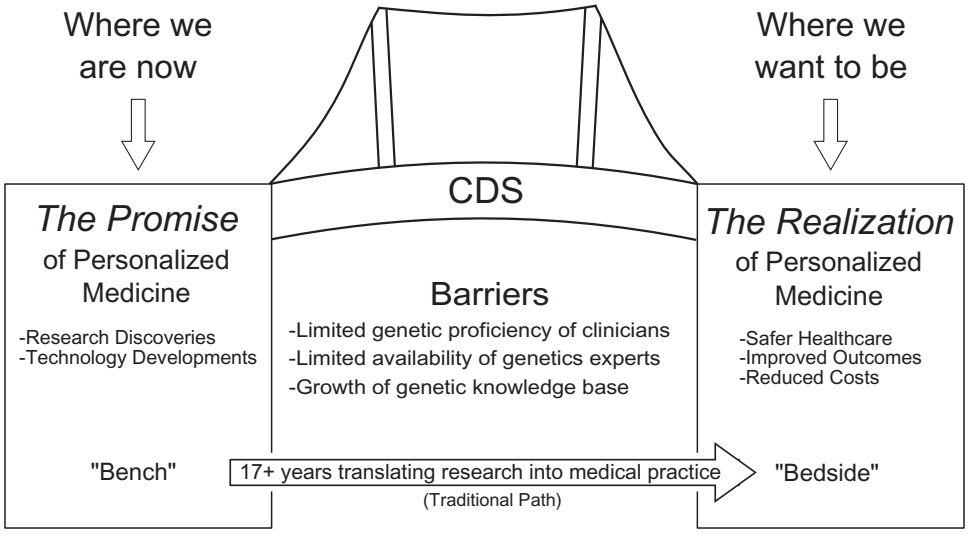

Figure 1 Clinical decision support (CDS) as bridge overcoming barriers to genetically guided personalized medicine.

Box 1 Manuscript inclusion criteria

- Definitions:
  - Healthcare provider = physician, nurse practitioner, physician assistant, registered nurse, or genetic counselor
  - Genetic factor = genotype, gene expression profile, and/or family health history
- Universal inclusion criteria:
  - English article
  - Human focus
  - Manuscript in peer-reviewed journal
- Additional inclusion criteria (at least one):
  - Intervention study evaluating the impact of a CDS system in an actual patient care context
    For a comparative intervention study, CDS required to be a part of the primary intervention under evaluation
    Excludes laboratory evaluations or simulation studies
  - Methodology article whose primary focus is on how CDS systems should be designed specifically to support clinical delivery of patient-specific assessments and/or recommendations guided by genetic factors. Includes system description articles.

to deliver genetically guided, patient-specific care guidance (figure 2). The final set of included manuscripts consisted of 38 primary research articles.[17–54] The manuscripts included were published from 1990 to 2011, with the majority of manuscripts published on or after 2007. Provided below is a summary and analysis of these earlier works, grouped primarily by CDS type and area of clinical focus.

CDS systems for genetically guided cancer management

Genetically guided cancer management was the focus of 22 primary research articles summarized in tables 1–4.[17–37 54] These manuscripts include six manuscripts related to the Risk Assessment in Genetics (RAGs) system for providing FHx-driven CDS (table 1),[17–21 54] six manuscripts on other FHx-driven CDS tools for breast cancer management (table 2),[22–27] four manuscripts on genotype-driven CDS tools for breast cancer management (table 3),[28–31] and six additional manuscripts on GPM CDS tools for non-breast cancer management (table 4).[32–37]

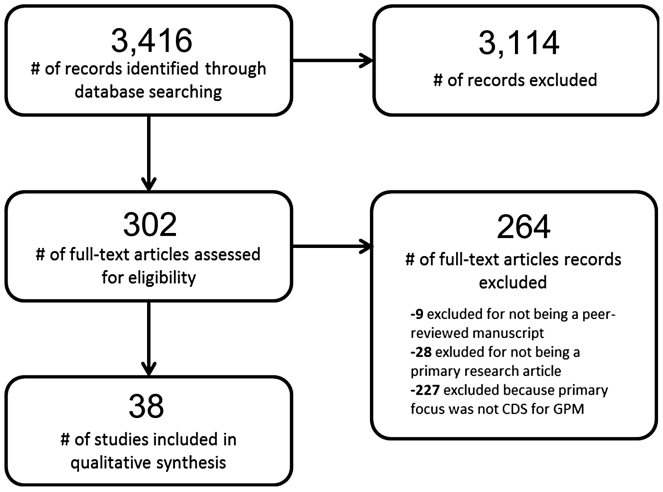

Figure 2 Manuscript selection process. CDS, clinical decision support; GPM, genetically guided personalized medicine.

RAGs system for providing FHx-driven CDS

Some of the earliest and most comprehensive research on the use of CDS to support GPM was conducted by Emery[55] (table 1), who identified that existing systems were not designed for primary care and that none provided patient management advice based on calculated risk. To address this gap, Emery developed a system known as RAGs, which helped general practitioners (GPs) in the UK collect FHx relevant to familial breast, ovarian, and colorectal cancer and provided appropriate management guidance, primarily regarding guideline-based specialist referrals.[17–19 54] A later extension of the RAGs system was referred to as the GRAIDS system.[20 21] This body of work included several favorable evaluations of these systems,[18 19 21] including a cluster randomized controlled trial (RCT) across 45 GP teams that found that GRAIDS significantly increased the proportion of patients referred appropriately to the regional genetics clinic according to evidence-based practice guidelines.[21]

Other FHx CDS tools for breast cancer management

Beyond the work of Emery,[55] CDS research for GPM has focused heavily on breast cancer management (table 2). Risk assessment tools for breast cancer can enable personalized care according to an individual's level of risk.[22 23] An RCT conducted in the UK found that a stand-alone breast cancer CDS tool had limited impact due to lack of awareness and use by GPs.[24] At the same time, a stand-alone CDS tool that calculated risks for breast cancer, heart disease, osteoporosis, and endometrial cancer was shown in an RCT to enhance the effectiveness of genetic counselors using the system.[25 26] Another stand-alone CDS system that has been found to be beneficial is HughesRiskApps, which collects relevant FHx information and provides clinicians with various tools to support the management of patients. An observational implementation study of this tool in a community hospital setting found significant adoption and impact.[27]

Genotype-driven CDS tools for breast cancer management

Several investigators have developed CDS systems that support treatment and decision-making once mutations have been identified in the breast cancer (BRCA) genes (table 3). In the UK, Glasspool and colleagues[30 31] developed a CDS tool known as REACT (Risks, Events, Actions and their Consequences over Time), which used a graphical timeline display to model real-time changes in lifetime risks as a result of risk-reduction interventions for breast cancer and ovarian cancer. In addition, several patient-directed, stand-alone CDS systems have been developed for improving risk communication and decision-making in breast cancer management based on BRCA genotype.[28 29]

CDS for other cancers

Besides breast cancer, other cancers have been the focus of CDS research and development (table 4). Most of this CDS research for other cancers has involved colorectal cancer, and in particular Lynch syndrome—a strongly heritable type of colorectal cancer.[32–34] Of note, the RAGs and GRAIDS systems described earlier supported both breast cancer and colorectal cancer management.[17–21 54] An additional CDS system investigated for colorectal cancer management is CRCAPRO, similar to BRCAPRO, which used FHx to identify patients at risk of hereditary colorectal cancer.[33] In addition, a group in the Netherlands developed a CDS intervention to remind pathologists to order Lynch syndrome genetic testing among patients

Table 1 Summary of primary research on CDS systems for cancer-related GPM: RAGs system for providing FHx-driven CDS

Citation and name of system (if applicable)	Manuscript summary and trial details (if applicable)	Users and study location	Genetic information used	Integrated with primary clinical information system	CDS purpose and clinical focus	Manuscript type	Notable informatics aspect
Coulson, 2001[17]; RAGs	System description of RAGs, which was designed to help GPs build a family pedigree, calculate genetic risk, and obtain guideline-based care recommendations	GPs in UK	FHx	No	Assessment of patient risk and provision of management recommendations for familial breast, ovarian, and colorectal cancer	System description	RAGs uses PROforma, an argumentation-based technology for CDS
Emery, 1999[18]; RAGs	A qualitative evaluation of RAGs, which found that the system was easy to use by GPs and served as an appropriate application of information technology to assist with clinical care	GPs in UK	FHx	No	Assessment of patient risk and provision of management recommendations for familial breast, ovarian, and colorectal cancer	Qualitative study	RAGs uses PROforma, an argumentation-based technology for CDS
Glasspool, 2001[54]; RAGs	System description of RAGs, which uses an argumentation approach to assess genetic risk and provide detailed qualitative explanation with referral advice	GPs in UK	FHx	No	Assessment of patient risk and provision of management recommendations for familial breast, ovarian, and colorectal cancer	System description	RAGs uses PROforma, an argumentation-based technology for CDS
Emery, 2000[19]; RAGs	Comparative analysis of RAGs, Cyrillic (a commercially available pedigree drawing system), and pen and paper for use by GPs. This study demonstrated that RAGs significantly improved pedigree accuracy and produced more appropriate management decisions than the other two methods. Furthermore, 92% of GPs preferred RAGs to the other methods	GPs in UK	FHx	No	Assessment of patient risk and provision of management recommendations for familial breast, ovarian, and colorectal cancer	Comparative study	RAGs uses PROforma, an argumentation-based technology for CDS
Emery, 2005[20]; GRAIDS	System description of GRAIDS, a next-generation FHx CDS tool that built on both RAGs and Cyrillic and provided an enhanced user interface for GPs to assess familial cancer risk	GPs in UK	FHx	No	Assessment of patient risk and provision of management recommendations for familial breast, ovarian, and colorectal cancer	System description	Server-based application that provides both heuristic and statistical risk assessment
Emery, 2007[21]; GRAIDS	A cluster RCT of GRAIDS conducted across 45 GP teams in the UK. GRAIDS significantly increased the number of referrals to the regional genetics clinic ($p=0.001$), with the referrals being significantly more likely to be consistent with referral guidelines ($p=0.006$). Moreover, patients referred from GRAIDS practices had significantly lower cancer worry scores at the point of referral ($p=0.02$)	GPs in UK	FHx	No	Assessment of patient risk and provision of management recommendations for familial breast, ovarian, and colorectal cancer	RCT	Server-based application that provides both heuristic and statistical risk assessment

CDS, clinical decision support; FHx, family health history; GP, general practitioner; GPM, genetically guided personalized medicine; GRAIDS, Genetic Risk Assessment in an Intranet and Decision Support; RAGs, Risk Assessment in Genetics; RCT, randomized controlled trial.

Table 2 Summary of primary research on CDS systems for cancer-related GPM: other FHx CDS tools for breast cancer management

Citation and name of system (if applicable)	Manuscript summary and trial details (if applicable)	Users and study location	Genetic information used	Integrated with primary clinical information system	CDS purpose and clinical focus	Manuscript type	Notable informatics aspect
Tsouskas, 1997[22]	Evaluation of a CDS tool that used patient-specific breast cancer risk information, including FHx, to identify patients at high risk of breast cancer. The system identified nine out of 10 women with breast cancers in this study	Clinicians in Europe	FHx	No	Assessment of patient risk for breast cancer	Validation study	Expert system developed using a variant of the BASIC programming language
Berry, 2002[23]; BRCAPRO	Evaluation of BRCAPRO, which predicted the probability of carrying a BRCA mutation based on a patient's FHx. BRCAPRO was effective in predicting the probability of carrying the BRCA mutation	Clinicians in USA	FHx	No	Assessment of patient risk for breast cancer	Validation study	Probability calculated using Bayesian updating
Wilson, 2006[24]	RCT of a stand-alone breast cancer CDS tool to guide referrals in everyday GP practices. The study consisted of 86 GP practices. The CDS system did not result in a statistically significant improvement, due largely to the limited awareness and adoption of the tool by GPs	GPs in UK	FHx	No	Assessment of patient risk and provision of management recommendations for breast cancer	RCT	The deployment of the CDS system was purposely pragmatic and did not involve extensive workflow integration measures
Matloff, 2007[26]	System description of a tool to provide patient-specific predictions of women's future risks for breast cancer, heart disease, osteoporosis, and endometrial cancer utilizing personal and FHx	Genetic counselors in USA	FHx	No	Assessment of patient risk for breast cancer	System description	System used a Markov model
Matloff, 2006[25]	RCT of a CDS tool used by genetic counselors[26] to enable personalized risk assessment and genetic counseling. The trial involved 48 cancer-free, post-menopausal women with a first-degree relative of breast cancer who were contemplating the use of alternative menopausal therapy options. This trial found that patients in the intervention group had increased knowledge and a lower, more accurate perceived risk of developing breast cancer compared to the control group	Genetic counselors in USA	FHx	No	Assessment of patient risk for breast cancer	RCT	System used a Markov model
Ozanne, 2009[27]; Hughes Risk Apps	System description of HughesRiskApps and evaluation of its impact at a community hospital. The CDS system significantly increased the number of patients seen for risk consultation and genetic test ordering. The implementation improved efficiency in several ways and did not require significant investment in capital or personnel	Clinicians in USA	FHx	No	Assessment of patient risk and provision of management recommendations for breast cancer	System description; pre–post comparison	Used tablet computers to collect information from patients. Used Health Level 7 compliant information models.

CDS, clinical decision support; FHx, family health history; GP, general practitioner; GPM, genetically guided personalized medicine; RCT, randomized controlled trial.

who met certain criteria, one of which was a suspicious FHx. This intervention significantly improved pathologists' recognition of patients at risk of Lynch syndrome.[34] Moreover, Dr Henry Lynch, for whom Lynch syndrome is named, developed a CDS system for supporting his hereditary cancer consulting service. This CDS system expedited clinicians' decision-making processes and resulted in a significant reduction in time spent on cases.[32]

Similar to the stand-alone CDS systems for breast cancer management described earlier,[28 29] stand-alone CDS tools have been shown to be useful for the management of other types of cancers, including prostate cancer[37] and alcohol-related

Table 3 Summary of primary research on CDS systems for cancer-related GPM: genotype-driven CDS tools for breast cancer management

Citation and name of system (if applicable)	Manuscript summary and trial details (if applicable)	Users and study location	Genetic information used	Integrated with primary clinical information system	CDS purpose and clinical focus	Manuscript type	Notable informatics aspect
Schwartz, 2009[28]	RCT of patient-facing tool that captured patient-specific information and provided tailored content about risks, benefits and management options based on the patients' particular situations. This study found that among 214 BRCA-positive women who were initially undecided about how to manage their breast cancer risk, patients who used the CDS tool were more likely to reach a management decision (p=0.001), had decreased decision conflict (p=0.002), and increased satisfaction (p=0.002) compared to women who did not use the CDS tool	Patients in USA	Genotype	No	Provision of management recommendations for breast cancer	RCT	CD-ROM based, patient-directed decision aid
Hooker, 2011[29]	Longitudinal RCT of patient-facing BRCA decision aid.[28] This study showed significantly higher cancer-specific distress (p=0.01) and genetic testing-specific distress (p=0.01) among users of the personalized decision aid after one month. Distress levels between groups were the same after 12 months	Patients in USA	Genotype	No	Provision of management recommendations for breast cancer	RCT	CD-ROM based, patient-directed decision aid
Glasspool, 2007[30]; REACT	System description of REACT (Risks, Events, Actions and their Consequences over Time), a breast cancer CDS tool with a graphical timeline display to model real-time changes in lifetime risk as a result of risk-reduction interventions such as tamoxifen therapy, hormone therapy, and mastectomy	Genetic counselors in UK	Genotype	No	Prediction of response to treatment for breast and ovarian cancer	System description	Graphical display of risk changes dynamically based on selected interventions
Glasspool, 2010[31]; REACT	Qualitative study of REACT by eight genetic counselors.[30] Most counselors found REACT effective for genetic risk management, although there were concerns related to the tool's potential to alter the dynamics of the clinician–patient interaction	Genetic counselors in UK	Genotype	No	Prediction of response to treatment for breast and ovarian cancer	Qualitative study	Graphical display of risk changes dynamically based on selected interventions

CDS, clinical decision support; GPM, genetically guided personalized medicine; RCT, randomized controlled trial; REACT, Risks, Events, Actions and their Consequences over Time.

cancers.[36] These studies included an RCT that showed that a patient-directed, genotype-driven CDS tool for alcohol-related cancer risk significantly reduced alcohol consumption by patients at increased genetic risk.[36] These studies, as well as the previous studies on breast cancer,[28 29] showed that patient-directed CDS systems can be clinically useful.

CDS for pharmacogenomics

Pharmacogenomics, the practice of tailoring drug therapy to the patient's unique genetic characteristics, can be a complicated process; genetically guided CDS offers a solution for simplifying this process. Table 5 summarizes the six primary research articles identified on this topic.[38–43] These studies include a description and validation of a CDS system for genetically guided treatment of HIV infections,[38] as well as an RCT that found that genotyping combined with CDS-guided therapy improved outcomes over standard of care.[39] Outside of HIV therapy, other investigators focused on how CDS for pharmacogenomics could be integrated with primary clinical information systems such as computerized provider order entry systems.[40 42 43] These studies evaluated considerations such as developing the underlying pharmacogenomics knowledge base,[40] representation of genetic information in the EHR for supporting pharmacogenomics CDS,[42] and the availability of patient data required for pharmacogenomics within the EHR.[43] The lone stand-alone system for pharmacogenomics used genotype and clinical data to estimate and graphically represent a patient's plasma warfarin concentration over time.[41]

Other CDS systems for GPM

Table 6 summarizes the 10 primary research articles that were neither cancer specific nor focused on pharmacogenomics.[44–53] As with CDS for cancer, there has been a substantial focus on FHx-driven CDS for other medical conditions. For example, a tool called GenInfer considered FHx and calculated inheritance risks for genetic diseases,[44] and FHx-driven CDS was included as a part of the National Russian Genetic Register.[45 46] Beyond these system descriptions, recent studies of FHx-driven CDS have focused on impact evaluation, with mixed results.[48 49 51]

Finally, there were four primary research studies on genotype-driven CDS systems not focused on pharmacogenomics or

Table 4 Summary of primary research on CDS systems for cancer-related GPM: CDS for other cancers

Citation and name of system (if applicable)	Manuscript summary and trial details (if applicable)	Users and study location	Genetic information used	Integrated with primary clinical information system	CDS purpose and clinical focus	Manuscript type	Notable informatics aspect
Evans, 1995[32]	Description of a FHx CDS system developed for a hereditary cancer consulting service. The system collected FHx information, evaluated the FHx for familial risk patterns, and produced preliminary risk assessment and management recommendations. The system resulted in a significant reduction in time spent on cases	Hereditary cancer consulting service in USA	FHx	No	Assessment of patient risk and provision of management recommendations for hereditary cancer	System description; impact observation	Expert rule-based system that modeled the pattern recognition capabilities of clinical geneticists
Bianchi, 2007[33]; CRCAPRO	Evaluation of CRCAPRO, which used FHx of colorectal and endometrial cancers to identify patients with Lynch syndrome. This study showed that CRCAPRO has low sensitivity and specificity	Clinicians in UK	FHx	No	Assessment of patient risk for colorectal cancer	System validation	Probability calculated using Bayesian updating
Overbeek, 2010[34]	RCT of electronic reminders to pathologists to consider Lynch syndrome genetic testing among newly diagnosed colon cancer patients based on FHx. The CDS reminder intervention in 12 pathology laboratories significantly improved pathologists' recognition of patients at risk for Lynch syndrome (OR 2.8; 95% CI 1.1 to 7.0) and increased use of genetic testing (OR 4.1; 95% CI 1.3 to 13.2)	Pathologists in Europe	FHx	Yes	Provision of management recommendations for colorectal cancer	RCT	Electronic reminders provided through health information system
Picone, 2011[35]; NeoMark	System description of NeoMark, a web-based tool that combined medical images, genetic markers, and other patient data before and after treatment of oral cavity squamous cell carcinoma to predict reoccurrence	Clinicians in Europe	Genotype	No	Assessment of patient risk for oral cancer	System description	Uses a service-oriented, modular architecture
Hendershot, 2010[36]	RCT of a web-based genetic feedback intervention involving 200 college students of Asian descent. The system provided personalized alcohol-related health risk information and feedback based on the patient's genotype. The tool resulted in significant reductions in drinking ($p=0.02$) among participants with the genotype associated with higher risk of alcohol-related cancer	Patients in USA	Genotype	No	Assessment of patient risk; reduction of risky behavior (alcohol consumption) for alcohol-related cancer	RCT	Web-based intervention
Wakefield, 2011[37]	System description and pilot usability test of an online CDS tool that presented 22 men with age and family history-specific prostate cancer risk information and management recommendations. Most participants preferred this method for receiving prostate cancer information	Patients in Australia/New Zealand	FHx	No	Assessment of patient risk and provision of management recommendations for prostate cancer	System description; pilot usability test	Online decision aid using a Markov model

CDS, clinical decision support; FHx, family health history; GPM, genetically guided personalized medicine; RCT, randomized controlled trial.

Table 5 Summary of primary research on CDS systems for pharmacogenomics

Citation and name of system (if applicable)	Manuscript summary and trial details (if applicable)	Users and study location	Genetic information used	Integrated with primary clinical information system	CDS purpose and clinical focus	Manuscript type	Notable informatics aspect
Pazzani, 1997[38]; CTSHIV	System description of the CTSHIV CDS program which manages HIV genome data and makes virus-specific therapeutic recommendations	Clinicians in USA	HIV genotype	No	Provision of management recommendations for HIV	System description	Uses a backward chaining expert system
Tural, 2002[39]; RetroGram	RCT of genotyping accompanied by RetroGram, which ranked drug suitability based on the HIV genotype. This study showed that genotyping combined with RetroGram use improved HIV therapy outcomes over standard of care ($p<0.05$)	Clinicians in Europe	HIV genotype	No	Provision of management recommendations for HIV	RCT	Contains approximately 200 rules based on the scientific literature
Swen, 2008[40]	Description of how the Royal Dutch Association for the Advancement of Pharmacy developed guidelines for the use of genetic information for drug prescribing and integrated these guidelines into automated drug prescription and medical surveillance systems for nationwide use	Clinicians and pharmacists in Europe	Genotype	Yes	Alert on gene-drug interactions for pharmacogenomics	System description	Recommendations incorporated into the G-standard, an electronic drug database used for CDS
Bon Homme, 2008[41]	System description of prototype CDS tool for personalized warfarin therapy that combined genetic and clinical data to estimate the required warfarin dose and the patient's plasma warfarin concentration	Clinicians in USA	Genotype	No	Therapeutic dose guidance for warfarin	System description	Provides a graphical display of estimated plasma warfarin concentration over time
Deshmukh, 2009[42]	This study compared the use of a single nucleotide polymorphism data model to the use of an allele data model for CDS computation in an EHR system. While there were statistically significant differences in computation time, this did not translate into significant differences in the overall clinician ordering time	Clinicians and pharmacists in USA	Genotype	Yes	Alert on gene—drug interactions for pharmacogenomics	Comparative study on genotype data representation	CDS rules developed within the Cerner EHR environment
Overby, 2010[43]	This study found that the Pharmacogenomics Knowledge Base was a good source for pharmacogenomics knowledge and that sufficient clinical data existed in the local EHR system to support 50% of the pharmacogenomic knowledge in drug labels that are capable of being expressed as CDS rules	Clinicians in USA	Genotype	Yes	Provision of therapy guidance for pharmacogenomics	Feasibility study	The MINDscape EHR system was used in the study

CDS, clinical decision support; CTSHIV, Customized Treatment Strategies for HIV; EHR, electronic health record; RCT, randomized controlled trial.

cancer.[47 50 52 53] These systems included a CDS system that retrieved genetic, radiological and clinical data from clinical information systems to provide guidance on intracranial aneurism management,[52] as well as a portable medical device that integrated clinical and genetic data to provide a diagnosis for rheumatoid arthritis and multiple sclerosis.[47] In addition, GeneInsight provides geneticists and other clinicians with patient-specific genetic testing reports, as well as notifications regarding updates to the presumed clinical significance of patients' previously identified genotype.[50] Finally, in a survey study, Scheuner and colleagues[53] found that clinicians felt their EHR systems could do much more to meet their needs related to GPM.

Trend analysis

Publication volume on CDS for GPM generally increased over time, with a majority published since 2007 (figure 3). While all publications before 2007 focused on stand-alone CDS, 32% of articles since 2007 focused on integrated CDS (figure 4). Likewise, while 13% of manuscripts before 2007 involved the use of genotype for CDS, 61% of manuscripts since 2007 have involved the use of genotype (figure 5). As noted earlier, a major focus of the literature in this domain has been on FHx CDS, pharmacogenomics, and CDS for cancer management.

DISCUSSION

Summary of findings

In order to learn from past research efforts and to guide future research into the use of CDS to enable GPM, we conducted a systematic review of the literature. Through a literature search spanning from 1990 to 2011, we screened 3416 manuscripts and included 38 primary research articles. A majority of these manuscripts was published from 2007 to 2011, with an

Table 6 Summary of primary research on GPM CDS systems for other conditions

Citation and name of system (if applicable)	Manuscript summary and trial details (if applicable)	Users and study location	Genetic information used	Integrated with primary clinical information system	CDS purpose and clinical focus	Manuscript type	Notable informatics aspect
FHx-driven CDS systems							
Harris, 1990[44]; GenInfer	System description of the GenInfer program, which used FHx information along with other inheritance factors to calculate genetic risks and probabilities of inheritance	Clinicians in USA	FHx	No	Assessment of patient risk for inherited disease	System description	Based on Pearl's algorithm for fusion and propagation in a probabilistic belief network
Kobrinskii, 1997[45] and Kobrinsky, 1998[46]; National Russian Genetic Register	Description of the information system used by Russia's federal genetics center to manage patients across Russia in need of genetics care. This system supported pedigree creation, cytogenetic analysis, risk assessment, and information support	Genetics specialists in Europe	FHx	No	Assessment of patient risk for inherited disease	System description	Utilized both server–client and local deployment models
Orlando, 2011[48]; MeTree	System description of MeTree, a tool that evaluates FHx and provides management recommendations regarding various heritable conditions for patients and clinicians. Also provides the protocol for a planned evaluation of the tool in North Carolina primary care clinics	Patients and clinicians in USA	FHx	No	Assessment of patient risk and provision of management recommendations for inherited disease	System description; evaluation protocol description	Patient-driven application that provides CDS as a printout
Rubinstein, 2011[49]; CDC Family Healthware	RCT with 3284 participants of the CDC Family Healthware tool, which provides personalized screening recommendations for multiple heritable conditions based on FHx. Both intervention and control groups showed improved adherence to screening recommendations compared to the baseline time period, but there was no significant difference between the intervention and control groups	Patients in USA	FHx	No	Assessment of patient risk and provision of management recommendations for inherited disease	RCT	A patient-directed, web-based tool
Wells, 2007[51]; PREDICT CVD-5	System description of a real-time CDS system that pulled clinical data from the EHR to calculate cardiovascular disease risk and provide risk management recommendations. A retrospective analysis found that including the patients' ethnicity and FHx into the risk assessment process substantially increased the number of patients eligible for drug treatment and lifestyle management	Clinician in Australia and New Zealand	FHx	Yes	Assessment of patient risk for heart disease	System description; retrospective analysis	Integrated with the MedTech practice management system
Genotype-driven CDS systems							
Iavindrasana, 2008[52]; @neurIST	System description of @neurIST, a CDS system which collects genetic data, radiological data, and clinical data from clinical information systems to provide CDS regarding intracranial aneurisms	Clinicians in Europe	Genotype	Yes	Provision of management recommendations for intracranial aneurism	System description	Uses a service- oriented, standards-based approach
Kalatzis, 2009[47]	System description of a point-of-care portable medical device that integrates clinical data with genetic data obtained from a miniature diagnostic system to produce a diagnosis for rheumatoid arthritis and multiple sclerosis	Clinicians in Europe	Genotype	No	Diagnostic assistance for arthritis and multiple sclerosis	System description	A combination of artificial neural networks, decision trees, and support vector machines was found to have the best performance

Continued

Table 6 Continued

Citation and name of system (if applicable)	Manuscript summary and trial details (if applicable)	Users and study location	Genetic information used	Integrated with primary clinical information system	CDS purpose and clinical focus	Manuscript type	Notable informatics aspect
Scheuner, 2009[53]	A survey of health professionals, genetics experts, and EHR developers regarding the ability of EHR systems to document, organize, and use FHx and genetic information	Clinicians in USA	FHx; genotype	Yes	Assessment of patient risk and provision of management recommendations for genetically-guided personalized medicine	Survey	EHRs were generally perceived as lacking the ability to support genomic medicine
Aronson, 2011[50]; GeneInsight	System description of GeneInsight, a platform that provides patient-specific genetic testing reports as well as notifications when the presumed clinical significance of genetic variants change for patients who have been previously tested	Geneticists and other clinicians in USA	Genotype	No	Provision of patient-specific genetic testing reports; notification of changes in clinical significance of genetic variants	System description	Is registered with the Food and Drug Administration as a class I exempt medical device

CDC, Centers for Disease Control and Prevention; CDS, clinical decision support; EHR, electronic health record; FHx, family health history; GPM, genetically guided personalized medicine; RCT, randomized controlled trial.

increasing shift in focus from FHx CDS to genotype-driven CDS, and from stand-alone CDS to integrated CDS. There have been nine RCTs of CDS interventions for GPM, but most CDS interventions for GPM have not yet been rigorously assessed for their clinical impact.

Strengths and limitations

As one important strength of this study, as far as we are aware, this work represents the first systematic review on CDS for GPM. As such, it contributes an important perspective on a topic that has the potential to have significant impacts in both clinical medicine and biomedical informatics. As a second strength, this systematic review was based on search strategies refined through previous systematic reviews on related topics.[14–16] Third, we searched Embase in addition to MEDLINE, so as to provide greater coverage of the international literature. Finally, in addition to providing a summary of relevant manuscripts, this review provides insights and trend analyses that show how this scientific field has developed over time and where the field appears to be headed moving forward.

In terms of limitations, this study does not provide a quantitative meta-analysis of the impact of CDS interventions for GPM. However, such a meta-analysis was not possible due to the limited number of outcome studies in this field and the heterogeneous nature of the various interventions and clinical domains. Second, we only included manuscripts written in English, which may have led to some relevant manuscripts being excluded that were written in a different language. Third, some relevant 2011 articles may not have been indexed by the time of our literature search and therefore erroneously excluded. However, a literature search update in June 2012 added less than 1% to the number of articles we had previously retrieved through March 2012, which suggests that this risk is low. Finally, there is a potential for publication bias with regard to the clinical trials included, in which studies with successful outcomes were more likely to be published than studies with unsuccessful outcomes. There was a potential indication of such a bias, in that seven of nine RCTs evaluated (77%) reported positive results, whereas the expected rate of positive results would more typically be in the range of approximately 60%.[56] However, given the limited sample size, the observed discrepancy may simply be due to chance. Moreover, as discussed next, the high rate of successful interventions may be partly explained by the fact that use of many of these systems was required by the study protocol, which improved the systems' likelihood of use and impact.

Consistency of trial findings with expected outcomes

In a previous systematic review of CDS RCTs, we identified the automatic provision of CDS as a part of routine clinical workflow to be a critical predictor of the success or failure of CDS interventions (adjusted OR of 112.1, $p<0.00001$).[14] While automatic provision of CDS was not a guarantee of success in this systematic review, a lack of this feature was associated with negative outcomes in all cases, generally due to the lack of use of the system.[14] Moreover, a later RCT specifically evaluating the importance of automatic provision of CDS directly confirmed this finding.[57]

On initial examination, the results of the present systematic review seemed to contradict this finding, as we found several RCTs in which stand-alone CDS interventions for GPM were not provided automatically as a part of routine clinical workflow but resulted in positive improvements in clinical practice.[21 25 28 29 36 39] However, in all but one of these RCTs,[21] use of the CDS system

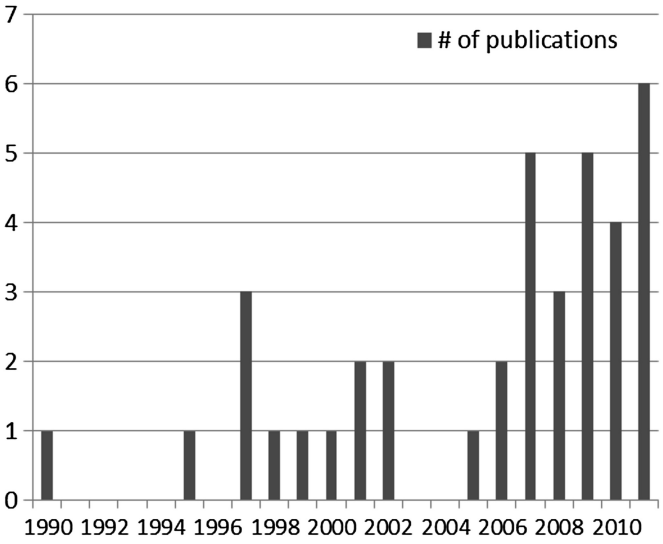

Figure 3 Publications included per year.

was mandated by the study protocol, which was an exclusion criterion in the previous systematic review that identified the critical importance of the automatic provision of CDS.[14] Therefore, we believe it is premature to draw the conclusion that automatic provision is not important when providing CDS for GPM, as it is possible that the same CDS interventions that led to positive results in the studies included would not have led to positive results if use of the system was not mandated by the study protocol, due to lack of awareness and use of the tool. With regard to other, less critical success factors identified in the previous systematic review of CDS interventions,[14] we did not find any trends that contradicted those findings. However, the sample size of available CDS trials was too small in this study to allow for any meaningful analysis of these other factors.

Of note, in the RCT of the GRAIDS system for FHx-based CDS, the system did have a positive impact, even though its use was not mandated by the study protocol and the system was not automatically provided as a part of routine clinical workflow.[14] However, the use and impact of this system may have been the result of exceptional circumstances specific to the study context and unlikely to be available in a routine clinical practice setting. In particular, in the RCT of the GRAIDS system, designated clinicians were recruited at each practice, received extensive training on GRAIDS, and managed all patients in the practice expressing concern regarding their breast or colorectal cancer FHx.[21] This type of resource-intensive deployment strategy may not be feasible outside the context of a research study, as demonstrated in another RCT of a stand-alone breast cancer CDS tool, which had limited impact due largely to the lack of awareness and adoption of the tool by clinicians.[24] Therefore, while more evidence is needed before a solid conclusion can be drawn, we found no conclusive evidence that CDS for GPM is unique in terms of the intervention features required for successful outcomes.

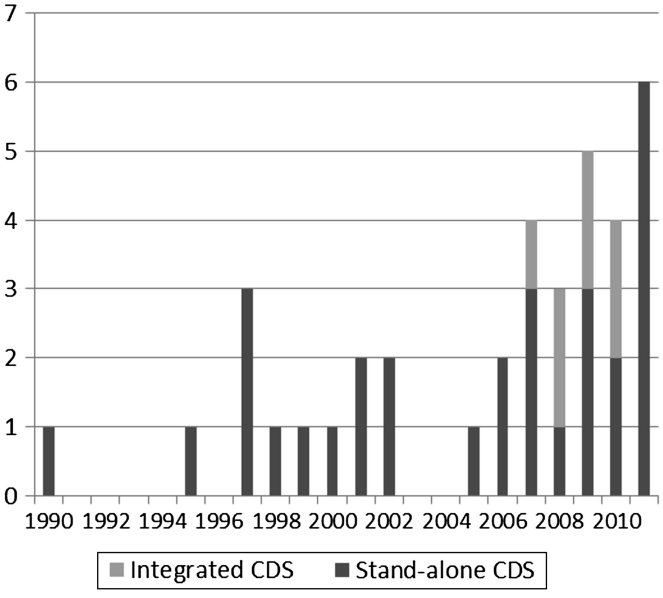

Figure 4 Publications focused on stand-alone versus integrated clinical decision support (CDS).

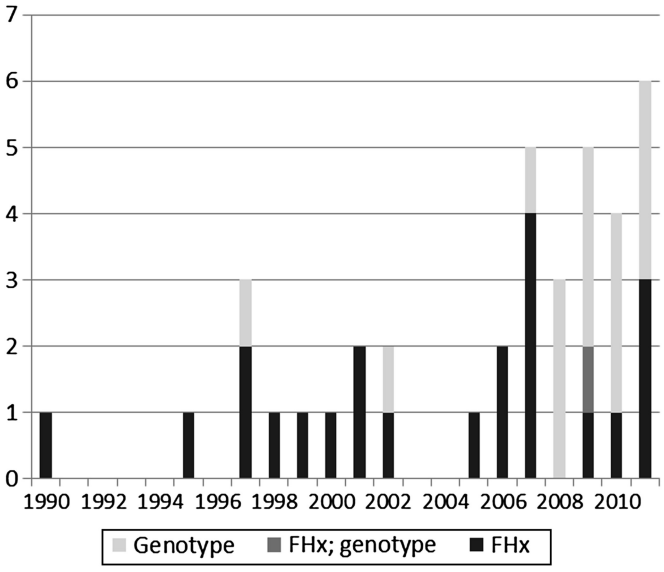

Figure 5 Publications focused on family health history (FHx)-driven versus genotype-driven clinical decision support.

Assessment of current research state and required research

In recent years, CDS has been proposed as a promising approach to realizing the promise of GPM.[10–12 58–65] However, we identified only 38 primary research articles published from 1990 to 2011 on the design, implementation, use, and evaluation of CDS systems to support genetically guided patient care, which amounts to approximately 1.7 articles per year. Even in the year with the most publications on this topic (2011), we identified only six primary research articles. In particular, we identified only nine RCTs of the impact of CDS systems for GPM, seven articles focused on CDS integrated with primary clinical information systems, and 16 articles involving the use of genotype to drive CDS. Furthermore, few groups have demonstrated how genotype-driven CDS can be integrated into clinical settings and clinical information systems in a scalable, standards-based, and effective manner.[40 43 52 53]

Given the tremendous volume of research being conducted in the discovery of novel personalized medicine diagnostics and therapeutics, we feel that much more research is required on how CDS can and should be leveraged to take these discoveries and to implement them in routine clinical practice. For example, even for FHx-driven CDS, which is perhaps the most well-

established area of research with regard to CDS for GPM, there has been limited research on the optimal use of FHx-driven CDS tools beyond hereditary cancer management. Indeed, given the limited literature available on any one topic, we feel it would be premature to consider any aspect of CDS for GPM to be fully mature and not in need of any further research.

In looking forward, we believe that the largest looming research challenge in terms of CDS for GPM will be the development of effective approaches to manage and utilize whole genome sequence data in the clinical setting. The pursuit of low-cost whole genome sequencing has been a priority research area for many years, such that sequencing costs may be reduced to a level amenable to routine clinical use in the near future.[66] While sequencing technologies continue to advance, the informatics capabilities to apply whole genome sequencing data to clinical practice is still in its infancy.[67] Indeed, in our systematic review, we did not find a single primary research article addressing this topic. Therefore, we recommend the prioritization and resourcing of this area of research by the scientific community. In particular, to realize the full clinical potential of whole genome sequence data, we believe that approaches will need to be developed for providing advanced CDS capabilities that are integrated with clinical information systems and provided automatically as a part of routine clinical workflow.

CONCLUSION

The promise of GPM is growing with the recent advances and discoveries in genomics research. With this growth also comes the growing need for translating such discoveries into everyday clinical care, so that we are able to realize the promises of GPM. CDS has the potential to bridge this gap between the promise and realization of GPM. By systematically reviewing the literature in this field and by identifying gaps in required research, we speculate that this paper will assist with efforts to leverage CDS to enable GPM at scale.

Contributors BMW and KK both contributed to the design and conduct of the study, as well as the preparation of the manuscript.

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Competing interests BMW is the founder and owner of SGgenomics, Inc., which developed ItRunsInMyFamily.com, a patient-centered FHx tool. KK is serving as a consultant to Inflexxion on a project funded by the National Institute on Drug Abuse to develop CDS capabilities for mental healthcare. KK receives royalties for a Duke University-owned CDS technology for infectious disease management known as CustomID that he helped develop. KK was formerly a consultant for Religent, Inc. and a co-owner and consultant for Clinica Software, Inc., both of which provide commercial CDS services, including through use of a CDS technology known as SEBASTIAN that KK developed. KK no longer has a financial relationship with either Religent or Clinica Software.

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Data sharing statement Individuals interested in the raw data and analyses may contact the corresponding author to obtain such data.

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