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Development, Implementation and Initial Results of CDSS Recommendations for Patients at Risk of Hereditary Breast Cancer

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Abstract

Breast cancer represents 23% of all cancers diagnosed among women each year. BRCA1 and BRCA2 are tumor suppressor genes related to the most frequent form of hereditary breast and ovarian cancer, as well as other types of cancer.

The aim of this work is to describe the development of Clinical Decision Support Systems (CDSS) for referral to genetic counseling in patients at increased risk of pathogenic variants in BRCA1 and BRCA2, and to describe results during the pilot study implementation (from January 5, 2021 to March 5, 2021).

To achieve integration and system interoperability, we used FHIR and CDS-Hooks within the CDSS development.

A total of 142 alerts were triggered by the system for 72 physicians in 98 patients. Results showed an acceptance rate for the recommendation of 2.1%, which could improve using intrusive alerts in all of the hooks.

Keywords:

Electronic Health Records; Genomics; Decision Support Systems, Clinical.

Introduction

Breast cancer is the most common type of cancer in women around the world. Each year, 1.15 million cases are diagnosed, representing 23% of all cancers diagnosed among women [1,2]. The greatest challenge is to identify preventive strategies that reduce the morbidity and mortality associated with this disease.

The discovery of BRCA1 and BRCA2 tumor suppressor genes has radically transformed our understanding of the genetic basis of breast cancer [3]. Germline mutations in BRCA1 and BRCA2 are responsible for 25% of the risk of familial breast cancer and therefore 5-10% of all breast cancers [4–6]. Breast cancer risk is not only increased in women but in men who harbor such variants as well [7].

In addition, pathogenic variants in BRCA1 and BRCA2 genes are associated with an increased risk of developing multiple types of tumors, such as cancer of the bile duct, bladder, esophagus, pancreas, prostate, stomach, melanoma, hematopoietic system, oral cavity or pharynx [8,9]. Pathogenic variants in BRCA1 and BRCA2 genes are the best-known genetic alterations involved in familial pancreatic cancer [10].

Identifying a hereditary cancer syndrome in the patient and/or his family, allows physicians to provide personalized care, cancer risk assessment, as well as preventive and screening strategies to reduce morbidity and mortality associated with the development of malignancies [7,11]. Genetic counseling may also be provided once a molecular diagnosis is established, since most forms of hereditary cancer, including BRCA variants, are autosomal dominant.

The molecular test for BRCA genes is recommended by the National Comprehensive Cancer Network (NCCN) of the United States in patients who meet at least 1 of 7 criteria based on age, sex, ethnic group, type of breast cancer and family and personal history of cancer. The decision to indicate the test in individuals with a personal or family history of cancer requires an individual risk assessment and genetic counseling. If the patient meets NCCN criteria and has been evaluated in genetic counseling consultations, a test limited to BRCA (either full gene sequencing or specific ethnic-oriented variant testing) or a multi-genetic panel may be considered [7,11,12].

Currently, the large amount of new information the physician must know in order to attend to patients appropriately, added to the limited time assigned to consultations in most healthcare scenarios, can lead to the generation of medical errors [13]. In this setting, Clinical Decision Support Systems (CDSS) can provide active help. These systems represent one of the greatest benefits of Electronic Medical Records (EHR). In addition, there is evidence that they can influence the test request behavior of physicians [14].

The aim of this work is to describe the development and first results, during the pilot study implementation, of CDSS for referral to genetic counseling in patients at increased risk of pathogenic BRCA1 and BRCA2 variants.

Methods

Setting

The Hospital Italiano de Buenos Aires (HIBA) is a non-profit healthcare academic center founded in 1853. It includes a network of two hospitals with 785 beds (200 for intensive care) and, approximately, 2,800,000 outpatient consultations per year. Since 1998, HIBA has run an in-house-developed health information system, which includes clinical and administrative data. It has been certified by the HIMSS as level 7 in the Electronic Medical Record Adoption Model, being the first hospital in Argentina to obtain this title. The EHR is a fully-implemented web based, problem oriented, patient centered record with customized functionalities depending on the level of care and terminology web services.

The HIBA Hereditary Cancer Program (ProCanHe) is a team made up of physicians who research, test and apply strategies for the promotion, prevention and treatment of hereditary cancers, including those linked to *BRCA1* and *BRCA2* genes.

HIBA worked together with genomIT, a multidisciplinary team of experts in health, data science and software development who apply personalized medicine through genetics and genomics, for the integration and advice on the use of genomic data in this project.

Development of the Rules

The risk criteria for pathogenic variants in *BRCA1* and *BRCA*2 genes were extracted from the NCCN. From this guide, four risk criteria were specifically used, which are the following:

- Diagnosis of breast cancer in women under 46 years of age.
- Diagnosis of breast cancer in men (regardless of age at diagnosis).
- Diagnosis of ovarian cancer (regardless of age at diagnosis).
- Diagnosis of pancreatic cancer (regardless of sex or age at diagnosis).

For each of these four criteria, a subset of problems was created, including all the pathologies associated with each condition. The reason for selecting these criteria is because they correspond to the patient's personal history. This type of data is registered more frequently in the patient's EHR than the patient's family history or other types of information, such as molecular characteristics of the tumor.

The CDSS take as input:

- The problems registered in the patient's problem list
- The physician's specialty
- The type of consultation, which must be scheduled previously.

On the other hand, the exclusion criteria are:

- The record of a previous genetic counseling interview.
- An already scheduled appointment with the genetic counseling team.
- An already performed genetic test.

The rule will not be activated again for a period of one year if the alert was previously rejected.

The CDSS were designed to be triggered in real time, after three different actions (hooks) [15] in the clinician's workflow on the EHR. These hooks are:

1. Patient-View (PV): when entering the patient's EHR (exclusive for general practitioners -GP-),
2. Condition-Create (CC): when creating problems in the patient problems list and
3. ProgressNote-Access (PNA): when performing a problem-based evolution.

In these particular cases the CDSS rules will be executed to evaluate if the patient meets the condition for increased risk for pathogenic variants in *BRCA1* or *BRCA*2 genes, and their referral to genetic counseling is pertinent.

The recommendation is aimed at GP of the following specialties:

- Family Medicine
- Internal Medicine
- Gerontology
- Oncology
- General Surgery
- Gynecology

The knowledge base (KB) has all the information needed to apply the risk criteria for pathogenic variants. It is represented with standard terminology.

Architecture and interoperability

To achieve the integration of the different systems, FHIR [16] and CDS-Hooks [17] standards were used.

The architecture of the solution was made up of the following main components (Figure 1):

1. The FHIR server.
2. The CDSS, which use Drools [18] for the rules and SNOMED-CT for model KB.
3. The EHR.

In each hook, the EHR searches the patient's clinical information in the FHIR standard in the FHIR server and then sends it to the CDSS. The CDSS will return the recommendations according to the CDS-Hooks standard. In turn, the EHR will report on the actions taken by the user on the recommendation for registration. The server is also capable of returning patient genomic information, from the institution's genomic database (Genomic Archiving and Communication Systems -GACS-), needed for specific rules that will be implemented in future versions. In this case FHIR Genomics is used.

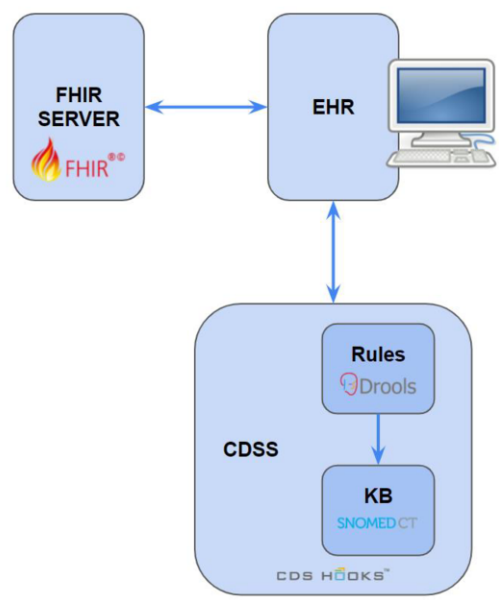

Figure 1 - Architecture of the CDSS at HIBA

Electronic Reminder

Once the physician is in the scheduled consultation, either in person or online with the patient, the alert differs depending on the role of the professional and the interaction with the EHR. In the case of specialists, when the physician is creating a problem (hook CC) or making a progress note associated to a problem (hook PNA) included in the corresponding subsets, the following image is shown in the header of the EHR (non-intrusive alert) (figure 2):

Figure 2 - Non-Intrusive Alert

When the physician clicks on the image, the interface in figure 3 is displayed.

When GPs access to the patient's EHR (hook PV) with problems from the aforementioned subsets, the alert appears directly with their options already displayed (intrusive alert) (Figure 3):

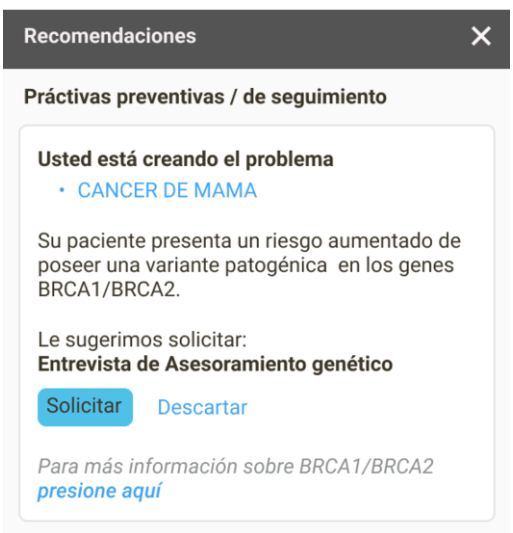

Figure 3 - EHR Alert Interface - intrusive alert

The pop-up has the following elements:

- The problem in the EHR
- A mention of the increased risk of having a mutation in the BRCA1 or BRCA2 genes.
- A suggestion for genetic counseling.
- Request or discard options for the recommendation.
- A link to a document with more information on hereditary cancer due to BRCA1 and BRCA2.

With the recommendation, the user can perform four main actions:

1. Accept
2. Reject
3. Close
4. Ignore

If the physician selects the "Request" option, a genetic counseling interview order is automatically created. In addition, a link with more information for the patient is offered with the steps to be followed, such as how to get an appointment or what information should be collected before the genetic counseling consultation (Figure 4).

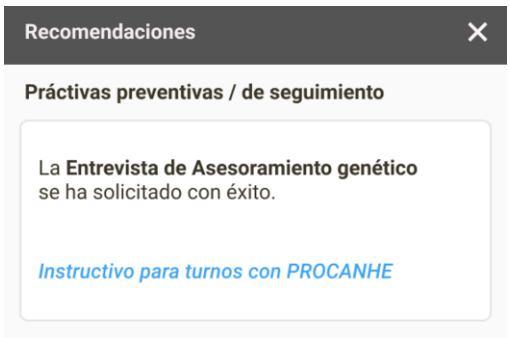

Figure 4 - Request Interface

If the professional selects the option "Discard" to reject the request, he/she must justify it by selecting one of the following options (Figure 5):

- The patient refuses genetic counseling.
- The order has already been requested by other means.
- The user disagrees with the recommendation.
- The patient is absent.
- The order will be requested in the next consultation.
- Other. With a free text field to complete.

The interface design was created in collaboration with the HIBA User Experience team, through iterative prototypes. The tool was tested for 2 weeks in a testing environment, where prototypes were corrected as needed.

Study design

Cross-sectional study, observational and descriptive, which included data from a pilot study. The CDSS were implemented on January 5, 2021. Pilot period lasted 3 months post-implementation, until April 5, 2021.

Data collection and statistical analyses

This research project was approved by the institutional review board. Confidentiality was guaranteed. There were no evident potential risks for patients.

We analyzed the following information:

- The total number of times the alert was triggered.
- The total number of physicians that interacted with the reminder.
- The total number of patients involved.
- The different types of interactions between physicians and the reminder.
- The different types of hooks that triggered the recommendations.

Results

A total of 142 alerts were triggered by the system for 72 physicians and in 98 patients.

Table 1 shows 101, 30 and 11 visualizations on PV, PNA and CC hooks, respectively. All the requests for genetic counseling interviews were made after the PV hook reminder activation.

Table 1– Results per hook

Hook	Total	Action				Effectiveness
		A	R	C	I	
PV	101	**3**	0	88	10	3%
PNA	30	0	0	0	30	0%
CC	11	0	0	0	11	0%
Total	142	3	0	88	51	2.1%

References: PV: Patient View, PNA: Progress Note Access, CC: Condition Create, **A**: Accepted, **R**: Refused, **C**: Closed, **I**: Ignored

A manual review of all patients with ignored and closed alerts was performed. It was found that three of them requested "Genetic Counseling Interview" outside the CDSS interface.

Since there were no rejections, the justifications for this action were not measured.

The Table 2 shows the medical specialties per alerts triggered, and the actions that physicians took.

Table 2– Medical specialities per alerts

Medical specialty	Total	Action				Effectiveness
		A	R	C	I	
Family Medicine	78	**2**	0	70	6	2.6%
Internal Medicine	19	**1**	0	14	4	5.3%
Gerontology	7	0	0	4	3	0%
Oncology	26	0	0	0	26	0%
General Surgery	0	0	0	0	0	-
Gynecology	12	0	0	0	12	0%

References: **A**: Accepted, **R**: Refused, **C**: Closed, **I**: Ignored

The diagnoses registered in the patient's EHR are shown in Table 3.

Table 3 – Diagnoses

Hook	Total	Action				Effectiveness
		A	R	C	I	
Breast CA F <46	42	1	0	32	9	2.4%
Breast CA M	4	0	0	3	1	0%
Ovarian CA	38	1	0	22	15	2.6%
Pancreatic CA	58	1	0	31	26	1.7%

References: CA: Cancer, F: Female, M: Male, **A**: Accepted, **R**: Refused, **C**: Closed, **I**: Ignored.

Discussion

This paper describes the development of an informatic tool created by a multidisciplinary team which was aligned with the organizational motivation, a recommended best practice in the discipline [19,20]. After implementation, initial results of an electronic reminder for patients at risk for BRCA pathogenic variants using CDSS triggered by the physician's workflow inside the EHR showed an effective rate of 2.1%.

Findings are similar with previous studies' estimations where as many as 96% of alerts are overridden [21–23]. Some have suggested that over time, alert override becomes habitual; this behavior is activated by environmental cues and repeated automatically, without conscious intention [24]. However, it is observed that this effectiveness varies according to the intrusiveness of the alert, the hook, the rule and the medical specialty [25]. All the accepted alerts corresponded to the PV hook, while in the PNA and CC hooks no acceptances were registered. This may be due to the fact that the alert in PV is intrusive, unlike the others.

Another reason to explain this low intervention rate could be that physicians may not be aware this tool exists or even know how to use the information within the CDSS [19].

Regarding the diagnoses, the cases of breast cancer in men have null effectiveness. This is mainly due to the low rate of alerts triggered by this diagnosis (4 out of 142), which is consistent with the low incidence of the disease in males [26]. In the rest of the pathologies, the effectiveness is balanced.

In relation to the medical specialties that interacted with the alerts, those that carry out a longitudinal follow-up of the patient's history, such as Internal Medicine and Family Medicine, were the ones that accepted the alert.

Although only three genetic counseling interview orders were made through the CDSS, we also observed the total number of patients in whom the alert was triggered, where another three patients attended the consultation with genetic counseling using a request not generated by the CDSS. Even though we cannot confirm physicians have read the content of the alert, we also cannot rule out they did not, influencing the final decision.

Of the total of three accepted alerts, only one effective genetic counseling interview was registered. We consider this could be explained by the current COVID-19 pandemic, which has led to the postponement of non-urgent medical consultations [27].

The main limitation of our study is the short period of time tested (three months), which could be not enough to obtain a greater number of cases and detect the completion of genetic counseling, nor to represent the real effective rate. As the next step, it could be necessary for CC and PNA hooks to trigger an intrusive alert, which will allow us to assess their impact on the care workflow and the test requests made.

In the future, we intend the genetic tests requested through our CDSS to contribute to feed the genomic database (GACS) of our institution. This genomic data would be used in a new CDSS with follow-up rules for patients with pathogenic variants.

Conclusions

The development of an electronic alert for patients at risk of BRCA mutations using CDSS could enhance patient care through personalized medicine, contributing to and accelerating the early detection of pathogenic variants in the *BRCA1* and

*BRCA*2 genes, for a huge impact on the patients and their families' health.

During the pilot study after implementation results showed an effective rate of 2.1%, which could be improved using intrusive alerts in all of the hooks.

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