

A Systematic Review and Meta-analysis of Complex Interventions to Increase Communication of Diagnosis of Genetic Condition to their Family Members and at-Risk Relatives

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Abstract

The diagnosis of genetic conditions leads to the identification of at-risk family members. However, communicating genetic conditions can be abstract and difficult to comprehend. Therefore, it is important that those who were diagnosed with genetic conditions need to be supported and encouraged to communicate their conditions to their family. The objective of the study is to summarize and examine the effects of complex interventions to increase the communication of genetic conditions to their family members. In searching for relevant studies, various bibliographic databases and Cochrane Library were used. Hand search and additional electronic searches were conducted from 1 January 2000 to 5 March 2017. Data extraction was based on the PRISMA recommendation. Included studies were critically appraised using evidence-based tools and systematically synthesized. Lastly, meta-analysis and sub-analysis were performed. The seven studies included in this review used a complex intervention to increase communication of those diagnosed with genetic conditions. The meta-analysis's overall result ($ORs=1.468$, $95\% CI=1.173-1.837$, $p<0.001$) was statistically significant. This study provided evidence regarding the complex intervention's effectiveness to encourage those diagnosed with a genetic condition to communicate this information to their family members or at-risk relatives.

Keywords: Communication, complex interventions, genetic conditions, genetic testing, systematic review, meta-analysis.

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INTRODUCTION

The diagnosis of a hereditary or genetic condition can lead to the identification of at-risk family members or relatives (Gallo *et al.*, 2009). In the current practice, those individuals who were diagnosed, tested, or undergoing genetic testing are the gatekeeper of the family's genetic information and has the responsibility to inform family and relatives (Daly *et al.*, 2016). However, in communicating genetic or hereditary conditions, information can be abstract and difficult to comprehend (Hamilton *et al.*, 2005). Thus, the task of communicating the information is difficult when there is no formal or proper training among those who will share the information (Metcalf *et al.*, 2008). This creates a problem together with the other issues families are facing at the same time (Foster *et al.*, 2004). Furthermore, it creates fear of how the communication dynamics within the family can hinder the effectiveness of transmitting information regarding their diagnosis of

hereditary conditions (Keenan *et al.*, 2005). Therefore, it is important that those who were diagnosed need to be supported and encouraged to communicate their conditions to their family members (Plumridge *et al.*, 2010). Through communication with their relatives, it helps them to be aware of the implication of this to themselves (Leenen *et al.*, 2015). However, this family communication is difficult to confirm because of the low prevalence of other family members presenting or consulting to genetic services for testing and management (Landsbergen *et al.*, 2005). Thus, it is important to have an overview and understanding of these dynamic relationships within family communication (Mendes *et al.*, 2015).

Through a good intervention to enhance the sharing of genetic conditions and discussing risks to other family members helps them to improve their perceptions and decision making in relation to their health (Daly *et al.*, 2016). However, there is limited

knowledge about the relationships between the characteristics and outcomes of intervention in improving communication in relaying hereditary conditions within the family (Montgomery *et al.*, 2013). It is essential to know the effectiveness of the interventions in the context of improving family communications among adults in relaying information regarding the diagnosis that is related to hereditary or genetics. Therefore, it is important to summarize all existing interventional research in relation to this area in an unbiased and thorough method (Ganeshkumar & Gopalakrishnan, 2013). Empirical research about communicating genetic risk in family pointed out that it is not a straightforward process (Lautenbach *et al.*, 2013). Those who were diagnosed acknowledge their responsibility to relay their condition and important information to their family members and relatives (Julian-Reyner *et al.*, 2000).

Family communication regarding the diagnosis of a hereditary condition is not a simple process but a complex one (Lautenbach *et al.*, 2013). It is important to have an intervention that is based on evidence to help individuals in facilitating the process of relaying complex genetic information that is relevant to other family members and relatives' health. Thus, this systematic review and meta-analysis of complex interventions to improve family communication were conducted. It aims to describe the types of interventions that have been developed and tested to increase the sharing of information to their family members and their effectiveness to assist practitioners and other researchers by providing them with summarized information to help them in helping an individual with a genetic condition to share this to their family members.

METHODS

Type of Studies

The type of studies eligible for inclusion in this review was published reports of primary research using quantitative randomized, non-randomized controlled trials or cohort studies. These quantitative studies to evaluate the effects of interventions that increased communication to the family regarding their conditions related to genetic conditions at varying stages and risks of the conditions or treatment to their adult family members or relatives published in the English language from January 2000 to March 2017.

Types of Participants

The participants in the study to be deemed eligible for inclusion in this review were adults (aged 18 and above) who have varying stages of risk and diagnosis related to genetic conditions.

Types of Interventions

Any intervention aimed to increase communication between adult patients who have varying stages of risks and diagnosis related to genetic

conditions and their adult family members or relatives regarding their condition.

Types of Outcome measures

The studies to be eligible for inclusion in this study reported either family members' intention to inform or to communicate or to talk about the condition or informed/communicated or talked about the condition to their adult family members or relatives after the intervention. Also, other outcomes of each of the studies included were explored such as behavioral changes, relatives contacted clinics, family members' coping mechanisms, etc.

Search Strategy

In this study, the method of conducting systematic reviews developed by the Centre for Reviews and Dissemination was adopted and followed (Centre for Reviews and Dissemination, 2009). In searching for relevant studies, a pre-tested and comprehensive step-by-step strategy was conducted. To locate these studies, bibliographic databases MEDLINE, EMBASE, Cumulative Index to Nursing and Allied Health Literature (CINAHL), PsycINFO and Cochrane Library were used. In addition, hand search and additional electronic searched using popular search engines were conducted after reviewing the reference list of the articles selected. The search was limited to published studies in English from 1 January 2000 to 5 March 2017. The Boolean operators "AND" and "OR" were used to combine free text terms and/or using medical subject headings (MeSH) to locate relevant studies. The following keywords were pre-tested and used to locate relevant studies: "family or famil*", "communication intervention", "genetic condition", "hereditary condition" and "familial condition". The flow of data selection was summarized in the flow diagram based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendation (Liberati *et al.*, 2009 and Moher *et al.*, 2009).

Data Collection

The review authors screened all the titles of the articles from the literature search and afterward screened the abstracts for its merits and relevance. The same authors assessed the studies for possible inclusion. The authors followed a systematic approach in the extraction of data based on the PRISMA recommendation (Liberati *et al.*, 2009) to produce a summary. The same review authors extracted relevant quantitative data from the included studies based on the pre-determined criteria. The qualitative data extracted were interventions, objectives, duration, and frequency of the intervention, major outcomes, and instruments used to measure the outcomes. In assessing the methodological quality, the following data were collected: the design of the study, recruitment methods of the participants, awareness of the study by the participants, allocation method, number of participants,

the proportion of followed up participants, analysis method and power calculation was conducted in the methodology. The data then was summarized in a table and a narrative overview of the findings was presented.

Data Analysis

In assessing the quality of the methodology of the included studies, the PEDro scale was used (López-de-Uralde-Villanueva *et al.*, 2016). This scale was derived from the Delphi list (Verhagen *et al.*, 1998). The internal and external validity of each of the studies was assessed according to the 11 criteria of the PEDro scale. The assessment of risk bias was assessed following the Cochrane Collaborations tool for assessing the risk of bias (Higgins & Green, 2013). The risk of bias was classified according to whether high, unclear, or low and the summary was presented in a table using the criteria from the Cochrane Handbook (Higgins & Green, 2013).

The studies included in the meta-analysis were those studies reported the frequency or proportion of participants in the intervention and control group arms who intended or communicated their genetic conditions to their family or relatives, or relatives visited the genetic centre. The 95% confidence interval (CI) and odds ratios (ORs) were computed from the proportions. The pooled ORs were computed and compared in both the control and intervention groups through a random-effects model. The random-effect model was selected over the fixed-effects model because it allows possible heterogeneity between the included studies during the analysis (Higgins & Green, 2013). Furthermore, analyses of subgroups were conducted to explore the possible effects of the differences in the details of the intervention on the outcome. The pooled ORs were computed using free open software, the Open Meta [Analyst], and the forest plot was generated using the same software (Wallace *et al.*, 2012).

RESULTS

Databases Search Results

The literature search using databases, hand searches, and the reference list of the included studies yielded a total of 5734 articles published in the English language from January 2000 to March 2017. Out of these published articles after reading the titles, 5599 articles were excluded, with the following reasons, duplicates, reviews, and commentaries, book chapters, not related to the topic and conference summaries or

abstracts. Out of 5734, 135 were considered for abstract reading. Seventeen papers were selected out of the 135 abstracts screened, and their full text was obtained. After reading the full text and using the pre-determined inclusion criteria, seven primary studies were selected to be included in this review for synthesis and meta-analysis. Figure 1 shows the flow chart on how the included studies were selected.

Characteristics of the Sample Participants

A total of 6302 adults with a mean age of 46.3 years old participated in the seven included studies from 2008 to 2016. 72% of the participants were female. The studies of Kardashian *et al.*, (2012), Montgomery *et al.*, (2013), and Bodurtha *et al.*, (2014) did not involve male participants. All the included studies involved adult participants and at-risk relatives diagnosed with various genetic or hereditary conditions. The genetic conditions were balanced chromosomal translocations, hereditary breast cancer (BRCA1 and BRCA2), ovarian cancer, hereditary non-polyposis, colorectal cancer, multiple endocrine neoplasias, hereditary heart diseases, diabetes, cystic fibrosis, fragile X conditions, lynch syndrome and spinal muscular atrophy (SMA). Table 1 shows a summary of the major characteristics of the sample participants in the included studies.

Description of the included studies

The included studies were six randomized controlled trials and one cohort study. Observable differences in the characteristics were evident in the selected studies in terms of the specific type of interventions evaluated; the type of participants; the implementation of the intervention, length of follow-up, instruments used to measure outcomes, and statistical techniques used to analyze data. Sample size ranging from $n = 146-3784$. All the included studies were explicitly indicated that the ethical review board or committee approved their respective study. The shortest follow-up was after two months (Kardashian *et al.*, 2012) and the longest follow-up was 2 years (Forrest *et al.*, 2008 and Hodgson *et al.*, 2016). All the studies included in this review described the recruitment process. The studies included did not explicitly indicate the intention-to-treat analysis approach for their statistical analyses. However, six studies appeared to include all the participants who were randomly allocated in each arm in their final statistical analysis. Table 2 summarized the main characteristics extracted from the included studies.

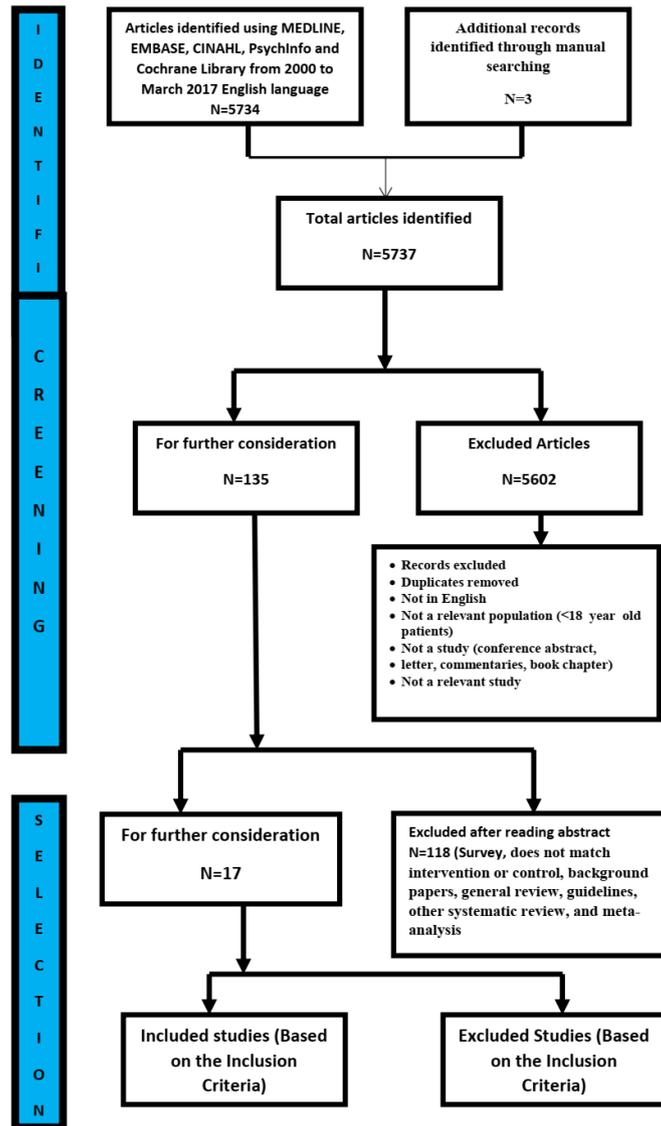


Figure 1: Flow chart in selecting included studies

Table 1. Summary of the main characteristics of the sample participants in the included studies.

Study	Sample size	Mean Age (Yr)	Male (%)	Female (%)	Type of Genetics or Hereditary Condition
Forrest et al., 2008	N=150	43.5	72 (48%)	78 (52%)	Balanced chromosomal translocation, hereditary breast and ovarian cancer (BRCA1 or BRCA2), hereditary nonpolyposis colorectal cancer, multiple endocrine neoplasia type 1, x-lined conditions
Roshanai et al., 2009	N=146	56	13(9%)	133 (91%)	Breast cancer, ovarian cancer and colorectal cancer
Kardashian et al., 2012	N=207	44.5	0%	207 (100%)	Breast cancer
Montgomery et al., 2013	N=345	48.5	0%	345 (100%)	Breast cancer and ovarian cancer
Bodurtha et al., 2014	N=490	33.4	0%	490 (100%)	Breast cancer and colon cancer
Wang et al., 2015	N=3784	50.6	1147(30%)	2637(70%)	Heart Diseases, Diabetes, Breast cancer, colon cancer and ovarian cancer
Hodgson et al., 2016	N=1180	47.6	563 (48%)	617 (52%)	Cystic fibrosis, fragile X conditions, inherited cancer (BRCA1, BRCA2, long QT syndrome, Lynch syndrome, balanced translocation carriers, and spinal muscular atrophy (SMA)
Total	6302	46.3	1795 (28%)	4507 (72%)	

Table 2. Characteristics of included studies

Study and Year	Country	Study Design	Objective	Intervention	Comparison	Outcome measured	Results
Forrest et al., 2008	Australia	Cohort Study	To determine the effectiveness of increased genetic counselling support could improve the uptake of genetic services by "at-risk" probands	An enhance genetic counselling using a specific discussion using a pedigree to identify at risk relatives about the importance of disclosure/communication then a follow up telephone call	General discussion about their genetic conditions and follow-up letter about the importance of disclosure to the family	Relative who made contact with genetic services	<ul style="list-style-type: none"> 61% (46/76) of at risk relatives had been definitely informed compared in the IG to CG 36% (20/55) with $X^2 = 6.52$, $p = 0.01$ after 2 years 54% (41/76) in the IG compared to CG 33% (18/55) went for genetic testing or made contact with genetic services w $X^2 = 6.41$, $p = 0.01$ after 2 years
Roshanai et al., 2009	Sweden	RCT	To investigate the effect of receiving extended cancer genetic information on counselee's knowledge, risk perception, information sharing and satisfaction with the service	Standard genetic counselling and met the specialist nurse who went through the given information in detail and communication skills, and received pamphlet, videotape, copy of medical records and copy of the pedigree to be used in communicating to their relatives	Standard genetic counselling and met specialist nurse and asked about their intention to inform at risk relatives and did not receive any further information	Participants informing relatives	<ul style="list-style-type: none"> After 8 months follow-up 73% (53/73) in IG and 73% (54/74) CG reported that they had informed all their relatives about their visit in cancer genetic clinic. X^2 statistic is 0.0025. The p-value is .95978. This result is not significant at $p < .05$
Kardashian et al., 2012	USA	Control and Intervention arms (RCT)	To determine the acceptability and feasibility of ShaRIT from the perspectives of study participants and genetic counsellors and to examine the rate of sharing BRCA results and family testing in relatives	ShaRIT (Sharing Risk Information Tool) is an educational genetic information tool and family resources organised in a binder given to BRCA carriers during the in-person results disclosure visit with genetic counsellors	Standard of care in-person genetic counselling visit to disclose BRCA results	Relatives eligible for sharing contacted by the participants	<ul style="list-style-type: none"> Relatives eligible for sharing BRCA results showed that 54% (72/134) from the CG were informed by the participants compared to 75% (55/73) in the IG after 2 months with Fisher exact test statistic is 0.002728. The result is significant at $p < .05$.

Table 2. Characteristics of included studies (continuation)

Study and Year	Country	Study Design	Objective	Intervention	Comparison	Outcome measured	Results
Montgomery et al., 2013	USA	RCT	To evaluate the efficacy of an intervention to prepare individuals to communicate BRCA1/BRCA2 results to family members	Genetic Counselling plus a communication intervention that was modelled on Robert Buckman's six-step strategy for communicating medical information (Buckman, 1992) and a resource guide and national action plan on breast cancer video	Counselling plus a wellness education intervention, list of websites containing nutritional information and national action plan on breast cancer video	Sharing the genetic test results to their family members or relative	<ul style="list-style-type: none"> 73% (136/187) in the IG shared their genetic test results to their family members compared to 70% (110/158) in the CG shared their genetic test results to their family members or relatives. Chi square test = 0.40, p = 0.52
Bodurtha et al., 2014	USA	RCT	To determine the effectiveness of KinFact intervention in increasing family communication about cancer history	Using KinFact (Keeping Information about Family Cancer Tune-up Program) Consist of a tailored risk information and prevention recommendations, review of pedigree using CAGene V.5.1 programme, identifying missing information in the family history, coach women in communication, and develop a plan for collection and follow-up information,	The control group was given a handout promoting ways to lower breast and colon cancer risk, screening, recommendation, and services contact information	Sharing and actively gathering information about familial cancer with relatives	<ul style="list-style-type: none"> The result showed that 24% (58/245) of the participants in the IG shared information to their relatives compared to the 15% (38/245) in the CG with OR=1.8 with 95% CI 1.1364- 2.8532 p= 0.01 after 14 months In actively gathering information about familial cancer 23% (59/245) in the IG compared to the CG of 14% (59/245) with OR=1.90 and 95% CI 1.1986 to 3.0221 and p= 0.006

Table 2. Characteristics of included studies (continuation)

Study and Year	Country	Study Design	Objective	Intervention	Comparison	Outcome measured	Results
Wang et al., 2015	USA	RCT	To examine Family Healthware™ intervention to increase family history awareness and documentation increase the extent to which this information is discussed within families and shared with health care providers	Family Healthware™- a web-based tool that assess familial risk and provides user with prevention plan which personalised suggestions of lifestyle changes and screening	Usual care, were not provided access to the tool, given general prevention messages, not tailored to familial risk	Communication with family members	<ul style="list-style-type: none"> Among those who were not communicating at baseline, IG were significantly reported communication with about family history, 34% (140/411) compared to CG 29% (74/254) OR = 1.24, 95% CI = 1.10-1.53, p=0.042 after 6 months
Hodgson et al., 2016	Australia	RCT	To determine the effectiveness of a complex genetic counselling intervention to improve family communication	A complex genetic counselling strategy to address documented personal barriers to family communication using reciprocal engagement Model, family history (pedigree analysis) and Telephone contact at 3, 6 and 12 months	Standard Care after diagnosis of genetic conditions	Relatives made contact with genetic services	<ul style="list-style-type: none"> Main outcome: 25.6% (142/554) of the relatives from the IG made contact to genetic services compared to 20.9% (112/536) in the CG, adjusted OR=1.30 with 95% CI 0.70-2.42, P=0.40 (NS) after 2 years Subgroup analysis: Low offspring risk (cystic fibrosis deafness, SMA) 12.3% in the IG compared to CG of 13.4 OR=0.91 95% CI 0.35-2.37, p 0.84, While on the High offspring risk (chromosomal translocations, fragile x-syndromes and SMA) 63.2% compared to 6.7% OR= 24 CI 3.42 to 168.47, p 0.001 after 2 years

Analysis of the risk of bias and methodological quality

The Cochrane criteria for the risk of bias analysis (Higgins & Green, 2013) and PEDro Scale (López-de-Uralde-Villanueva *et al.*, 2016) were useful in the appraisal of the methodological quality. Six

studies (Roshanai *et al.*, 2009, Montgomery *et al.*, 2013, Kardashian *et al.*, 2012, Bodurtha *et al.*, 2014, Wang *et al.*, 2015 and Hodgson *et al.*, 2016) have low risk in the domain on random sequence bias. The six studies described their methodology in generating the allocation sequence in good detail. The five RCTs

(Roshanai *et al.*, 2009, Montgomery *et al.*, 2013, Bodurtha *et al.*, 2014, Wang *et al.*, 2015 and Hodgson *et al.*, 2016) were classified as low risk in the domain of allocation concealment. The five RCTs explicitly indicated their allocation concealment. However, although they indicated that they perform allocation concealment, there is not enough information mentioned regarding how, or what method used to conceal the allocation sequence. Furthermore, it was unclear whether Kardashian *et al.* (2012) considered allocation concealment during the allocation of participants in the intervention and control arm of the study.

In the methodologies of Forrest *et al.*, (2008), Kardashian *et al.*, (2012), and Hodgson *et al.*, (2016) there was no indication that blinding of the participants and personnel was considered as part of the overall design. These studies were unclear in the domain of performance bias. The studies of Roshanai *et al.*, (2009), Montgomery *et al.*, (2013), and Wang *et al.*, (2015) explicitly indicated blinding among the counselors. Bodurtha *et al.*, (2014) indicated that blinding of the participants or the personnel was not considered before or during the implementation of the

intervention. The study of Forrest *et al.*, (2008), Roshanai *et al.*, (2009), Kardashian *et al.*, (2012) Montgomery *et al.*, (2013) and Hodgson *et al.*, (2016) considered being unclear in the domain of detection bias. These studies did not describe the blinding of the assessor and there is not enough information if any intention to blind the assessors or data collector from the knowledge whether the participants were allocated to the intervention or control group. Bodurtha *et al.*, (2014) was considered high risk as to the study indicated that blinding of the statistician was not considered. However, it was acknowledged as part of its major limitation in the interpretation of the result.

In the domain of attrition bias, the study of Forrest *et al.*, (2008), Roshanai *et al.*, (2009), and Kardashian *et al.* (2012) were considered low risk in this domain with attrition rate from 0% to 5%. On the other hand, Montgomery *et al.*, (2013), Bodurtha *et al.*, (2014), Wang *et al.*, (2015) and Hodgson *et al.*, (2016) were considered high risk with attrition rate from 21% to 37%. Table 3 provided the methodological quality using the PEDRo scale, the studies were considered good to excellent based on the 11 item points.

Table 3. Summary of the PEDRo score of all the included studies

Study	Specified Study Eligibility Criteria	Random Allocation of Subjects	Concealed Allocation	Similarity Between Groups at Baseline	Subject Blinding	Counselor Blinding	Assessor Blinding	Less than 20% Dropouts ^a	Intention to treat analysis ^b	Between-group statistical comparisons	Point measures and variability data	Total Score
Forrest <i>et al.</i> , 2008	1	0	0	1	0	0	0	1	1	1	1	6
Roshanai <i>et al.</i> , 2009	1	1	1	1	0	1	0	1	1	1	1	9
Kardashian <i>et al.</i> , 2012	1	1	0	1	0	0	0	1	1	1	1	7
Montgomery <i>et al.</i> , 2013	1	1	1	1	1	0	0	0	0	1	1	7
Bodurtha <i>et al.</i> , 2014	1	1	1	1	0	1	0	0	1	1	1	8
Wang <i>et al.</i> , 2015	1	1	1	1	0	1	1	0	1	1	1	9
Hodgson <i>et al.</i> , 2016	1	1	1	1	0	0	0	0	1	1	1	7

a. Based on the recommendation by Valentine & McHugh (2007)

b. Based on the denominator used to compute the outcome or explicitly stated in their methodology

Description of the complex interventions

All studies used complex interventions to increase communication of those who were diagnosed with hereditary conditions. These complex interventions consist of three or more elements. These interventions were tailored to individual participants. However, there was a contradicting outcome among the included

studies. Four studies (Forrest *et al.*, 2008, Kardashian *et al.*, 2012, Bodurtha *et al.*, 2014 and Wang *et al.*, 2015) demonstrated statistically significant results, while the three studies (Roshanai *et al.*, 2009, Montgomery *et al.*, 2013) and Hodgson *et al.*, (2016) did not reach a statistically significant result. Table 4 summarized the

elements of the complex interventions of each study included.

Table 4. Summary of the elements of the complex family communication intervention of all the included studies

Study and Year	Face to Face Education/Counselling	Use of Family History or Pedigree	Buckman's six steps	Telephone Follow-up	Printed Materials/ Handouts/ information Letter	Computer or Electronic Resources	Online or Website Resources
Forrest et al., 2008	Yes	Yes	No	Yes	No	No	No
Roshanai et al., 2009	Yes	Yes	Yes	No	Yes	No	No
Montgomery et al., 2013	Yes	Yes	Yes	No	Yes	No	No
Kardashian et al., 2012	Yes	Yes	No	No	Yes	Yes	Yes
Bodurtha et al., 2014	Yes	Yes	No	No	Yes	Yes	No
Wang et al., 2015	No	Yes	No	No	Yes	Yes	Yes
Hodgson et al., 2016	Yes	Yes	No	Yes	No	No	No

Meta-analysis

Overall pooled estimate

The overall meta-analysis of all included studies comparing complex intervention to the usual standard of care in increasing communication to family members or at-risk relatives was performed to show the overall relationship using *ORs*. The pooled *ORs* were computed based on the proportion of participants who intended or communicated, or relatives visited genetic clinics for testing as a proxy in sharing or communicating a genetic diagnosis. In the meta-

analysis, the result showed that the overall pooled effect of the intervention was statistically significant ($p < 0.001$) in increasing the communication to their family members or at-risk relatives over the usual standard of care. The overall pooled *ORs* = 1.468 with a 95% *CI* (1.173-1.837) and *I*² statistic = 38.1% ($p = 0.138$) in the intervention group receiving a complex intervention tailored to the individual compared to the control group receiving the usual standard of care. See Figure 2 for the Forest plot overall meta-analysis of all the studies included.

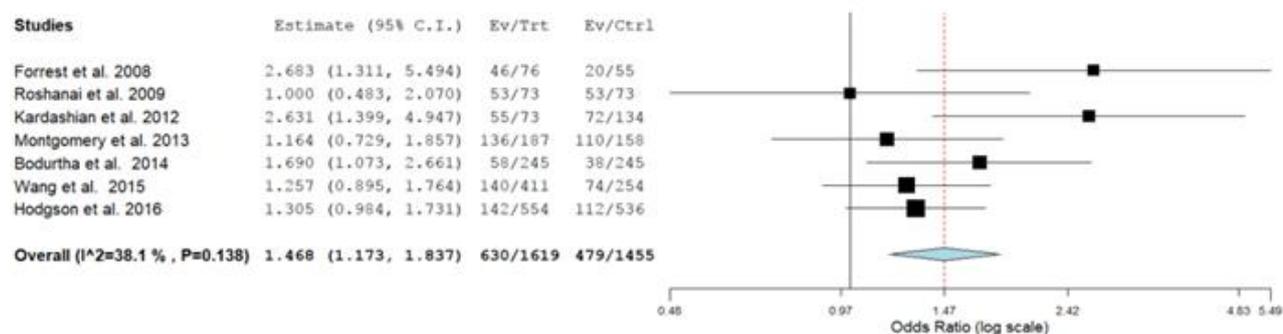


Figure 2. Forest plot of the overall meta-analysis of all the included studies

Subgroup meta-analyses

Face-to-face education and genetic Counselling

In using the face-to-face education and genetic counseling as a component of a complex intervention showed that the pooled *ORs* = 1.545 with a 95% *CI*

(1.171 -2.039) was statistically significant ($p=0.002$) and with $I^2=44.81\%$ ($p=0.107$).

Family health history or pedigree

Family health history or pedigree is an important tool for health communication, genetic testing interpretation, and interaction between patients and health care providers (Bodurtha *et al.*, 2014). There were contradicting results among the included studies. Four studies demonstrated a statistically significant result when family health history was used as part of their complex intervention. The proportion of participants range from 34%-75% in the intervention group compared to control group with 15%-54% communicated to their family members or relatives (Forest *et al.*, 2008, Kardashian *et al.*, 2012, Bodurtha *et al.*, 2014 and Wang *et al.*, 2015). On the other hand, the study of Roshanai *et al.*, (2009), Montgomery *et al.*, (2013), and Hodgson *et al.*, (2016) did not reach a statistically significant result. However, the pooled $ORs=1.468$ with a 95% CI (1.173-1.837) showed the effect was statistically significant ($p<0.001$) and $I^2=38.1\%$ ($p=0.138$).

Buckman's six steps communication strategy

Two studies (Roshanai *et al.*, 2009 and Montgomery *et al.*, 2013) added Buckman's six steps communication strategy. The sub-analysis showed that the pooled $ORs=1.113$ with a 95% CI (0.751-1.650). Both studies were statistically not significant in comparing the intervention group over the control group. The studies showed that the effect was statistically not significant ($p=0.593$) and $I^2=0\%$ ($p=0.731$).

Telephone for follow-up

Two of the included studies (Forrest *et al.*, 2008 and Hodgson *et al.*, 2016) added the user of telephone to follow-up and reiterate the importance of sharing genetic test results. The sub-analysis of the telephone follow-up as an element showed that the pooled $ORs=1.730$ with a 95% CI (0.868-3.449) was statistically not significant ($p=0.119$) with $I^2=70.3\%$ ($p=0.067$).

Printed materials

Five studies (Roshanai *et al.*, 2009, Kardashian *et al.*, 2012, Montgomery *et al.*, 2013, Bodurtha *et al.*, 2014 and Wang *et al.*, 2015) added the used of printed materials, handouts or information letter to reiterate the importance of sharing genetic diagnosis to family members or at-risk relatives. The sub-analysis of the use of printed materials showed that the pooled $ORs=1.429$ with a 95% CI (1.084-1.886) was statistically significant ($p=0.011$) with $I^2=36.58\%$ ($p=0.177$).

Computer or Electronic Resources

The studies of Kardashian *et al.*, 2012, Bodurtha *et al.*, 2014 and Wang *et al.*, 2015 added computer or electronic resources to enhance communication. The sub-analysis showed that the pooled $ORs=1.655$ with a 95% CI (1.120-2.444) was statistically significant ($p=0.011$) with $I^2=53.58\%$ ($p=0.116$).

DISCUSSION

This systematic review, adhered to the structured and transparent method recommended to search, identify, and synthesize available evidence on the effectiveness of complex interventions to increase communication to their family members and at risk-relatives regarding their genetic conditions or genetic test results. Six RCTs and one prospective cohort study were found and met the inclusion criteria for this review. The RCTs included in this review provide the highest evidence in the hierarchy of evidence to determine the cause-and-effect relationship between the intervention and the outcome (Higgins & Green, 2011). However, it was decided to include quantitative non-randomized designs in this review, to allow a more extensive and complete assessment of all the possible evidence on this topic, in line with the awareness that RCT design may not be applicable in some settings and situations (Rosen *et al.*, 2006).

The findings of all the studies are somewhat difficult to interpret and synthesize due to inherent issues within the design of the individual studies, heterogeneity of the designs of the complex interventions and the standard of care as a comparison, sample participants, measured outcomes, various assessment tools used to measure the outcomes and their respective methodological ways of analyzing the results. The difficulty in the interpretation of the synthesis of complex interventions is not uncommon and was indicated in other studies, for example in the study of Ranmal *et al.*, (2012). Despite the identified issues, using a critical and systematic approach in the analysis of and using evidence-based tools, this review presented evidence about the effects of a complex intervention to increase the communication to their adult members and at-risk relatives are considered strong and conclusive.

In this review, the complex interventions were described as an intervention consist of three or more elements that could be tailored to individual needs and could be delivered differently according to who implemented the intervention. Due to the complexity of the design of the interventions, it is difficult to determine which of the elements or combination of these elements significantly contributed to the effect of this intervention to the participants, However, by using sub-analysis of each of the components of the complex intervention using meta-analytic technique this presented evidence that a complex intervention with

face-to-face, genetic counseling, family health history or family pedigree, and provision of printed materials and computer or electronic resources proves to be effective in increasing the communication of genetic diagnosis to family members or at-risk relatives. Despite, two included studies did not reach statistically significant results from their studies, the overall weighted meta-analysis showed that this type of intervention was beneficial with an overall pooled effect of $ORs=1.468$ with $p < 0.001$.

However, even with an increase in the communication of those who were assigned in the intervention group compared to the control group due to the complex interventions, it appears that likely that there will be individuals who will remain silent, reluctant or unable to communicate their genetic diagnosis to their family members or at-risk relatives. For example, in the studies of Bodurtha *et al.*, (2014), Wang *et al.*, (2015) and Hodgson *et al.*, (2016), more than 70% of the participants in the intervention group did not communicate or shared their genetic diagnosis to their family members or at-risk relatives 6 months to 2 years post-intervention which is quite a significant proportion in comparison to those who communicated in the intervention group. A kind of intervention tailored to the needs of the participants makes it difficult to determine exactly what kind of intervention is most effective and for whom. In some studies, a complex intervention might not be effective overall but might have affected the subgroup of the participants such as the outcome in the sub-analysis in the study of Hodgson *et al.*, (2016).

Communicating health problems to family members and relatives is a complex and dynamic process (Daly *et al.*, 2016). Furthermore, there are unspoken rules among family on how communication within the family and with relatives regarding health and ill health (Rosland *et al.*, 2012). A non-disclosure of genetic diagnosis is a failure of communication that may be attributed to poor communication within the family or might be affected by the emotional closeness or distance from some at-risk relatives (Gaff *et al.*, 2008). Thus, when deciding on how to share information with family or at-risk relatives it is important to identify the central figure in the family during communication training among participants (de Geus *et al.*, 2014). As this may weigh in the factors and might affect the outcome.

Six out of the seven included studies in this review were all well-conducted RCTs, which considered to be the gold standard in evaluating interventions. However, the results of these RCTs may not reflect the real situation for patients and their relatives because of the inherent characteristics of how they select their population in unusual, controlled settings. Furthermore, despite that, the outcomes of systematic reviews and meta-analysis were considered

the most accepted source of evidence for policy and clinical decision-making processes. Thus, this adds to the possible limitation in interpretation and generalization of the results when these RCTs were synthesized using systematic review and meta-analysis. Furthermore, the complex interventions that were tested might have varying results in different countries, different cultures, and different health care set up.

CONCLUSION

In conclusion, this systematic review and meta-analysis provided additional literature and evidence regarding the effectiveness of complex intervention or strategy to encourage those who have genetic conditions or received a genetic test result to share or communicate this information to their adult family members or at-risk relatives. Seven studies met the inclusion criteria for synthesis and meta-analysis.

Overall, the included studies in this review were considered good to excellent methodological quality using both the risk of bias analysis described by Higgins & Green (2013) and the PEDRo scale. All the included studies used a complex intervention to increase communication of those who were diagnosed with genetic conditions and compared with the standard care provided after the diagnosis of genetic conditions. These complex interventions consisted of three or more elements to increase communication of information to their family members or relatives at-risk. The common elements in the complex interventions in most of the included studies were face-to-face education, genetic counseling, family health history, telephone follow-up, printed materials, and provisions of computer or electronic resources, use of Buckman's six-step communication strategy, and lastly, online resources.

Despite the contradicting outcome among the included studies. The four studies demonstrated statistically significant results, while the remaining three studies did not reach to provide a statistically significant result to show that a complex intervention is beneficial in increasing the communication of information. However, the overall result of the meta-analysis was statistically significant ($p < 0.001$). While on the sub-analysis of the components or elements of the complex interventions, face-to-face and genetic counseling ($p=0.002$), family health history ($p < 0.001$), printed materials ($p=0.011$), computer or electronic resources ($p=0.011$) were statistically significant. On the other hand, telephone follow-up, Buckman's six-step communication strategy, and the use of online resources were statistically not significant.

Although only seven studies were included, and despite the identified limitations of this review, the results of this systematic review and meta-analysis provided evidence indicating the effectiveness of a complex intervention with three or more elements in

increasing the communication of genetic diagnosis to their family members and at-risk relatives.

Conflict of Interests

I declared that this research has no conflict of interest. I have not received any funding from any organization when this research was conducted.

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