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A Clinical Decision Support Tool to Predict Cancer Risk for Commonly Tested Cancer-Related Germline Mutations

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Abstract

The rapid drop in the cost of DNA sequencing led to the availability of multi-gene panels, which test 25 or more cancer susceptibility genes for a low cost. Clinicians and genetic counselors need a tool to interpret results, understand risk of various cancers, and advise on a management strategy. This is challenging as there are multiple studies regarding each gene, and it is not possible for clinicians and genetic counselors to be aware of all publications, nor to appreciate the relative accuracy and importance of each. Through an extensive literature review, we have identified reliable studies and derived estimates of absolute risk. We have also developed a systematic mechanism and informatics tools for (1) data curation, (2) the evaluation of quality of studies, and (3) the statistical analysis necessary to obtain risk. We produced the risk prediction clinical decision support tool ASK2ME (All Syndromes Known to Man Evaluator). It provides absolute cancer risk predictions for various hereditary cancer susceptibility genes. These predictions are specific to patients' gene carrier status, age, and history of relevant prophylactic surgery. By allowing clinicians to enter patient information and receive patient-specific cancer risks, this tool aims to have a significant impact on the quality of precision cancer prevention and disease management activities relying on panel testing. It is important to note that this tool is dynamic and constantly being updated, and currently, some of its limitations include (1) for many gene-cancer

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Compliance with Ethical Standards

Conflict of Interest Dr. Hughes receives Honoraria from Myriad Genetics Veritas Genetics, Advisory Board for Beacon (An RFID Biopsy Marker), and is a founder of and has a financial interest in Hughes Risk Apps, LLC. Dr. Hughes's interests were reviewed and are managed by Massachusetts General Hospital and Partners Health Care in accordance with their conflict of interest policies. Dr. Parmigiani is a member of the Scientific Advisory Board and has a financial interest in Cancer Risk Apps LLC (CRA). CRA commercializes software for management of patients at high risk of cancer. At the present time, CRA is not supporting or licensing ask2me. We feel there is no significant overlap with this work.
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Human Studies and Informed Consent This article does not contain human subjects.

Animal Studies No animal studies were carried out by the authors for this article.

associations risk estimates are based on one study rather than meta-analysis,(2) strong assumptions on prior cancers, (3) lack of uncertainty measures, and (4) risk estimates for a growing set of gene-cancer associations which are not always variant specific. All of these concerns are being addressed on an ongoing basis, aiming to make the tool even more accurate.

Keywords

Germline mutation; Disease susceptibility; Genetic predisposition to disease; Risk assessment; Risk management

Introduction

Until recently, patients with hereditary cancer susceptibility predisposition were tested for only a few well-known and studied genes, usually related to a single syndrome. For example, women at high risk of breast or ovarian cancer were tested only for *BRCA1* and *BRCA2*. The rapid drop in the cost of DNA sequencing, as well as the over-turning of patents, have led to the availability of multi-gene cancer panels, which test a large number of genes at a relatively low cost (Plichta et al. 2016). These panels can test 25 or more cancer susceptibility genes at a time, often at a lower cost than previous single syndrome testing.

Following testing, patients rely on providers to interpret results, assess risk of various cancers, and advise on a management strategy. Evidence on the types of cancer associated with these genes, and the magnitude of the risk, is emerging rapidly (Couch et al. 2014; Desmond et al. 2015; Maxwell et al. 2014; Plichta et al. 2016; Tung et al. 2015, 2016a, 2016b; Walsh et al. 2011). However, the number of gene-cancer associations is large, information is dispersed over a vast number of studies, the quality of the studies is uneven, and the data presented are seldom directly applicable to patient care (e.g., one may find hazard ratios instead of the necessary absolute risk estimates). In an environment in which there is constant pressure to increase efficiency and see more patients, it is very challenging for clinicians to be aware of all publications, nor to appreciate the relative accuracy and importance of each. In addition, new information is becoming available on almost a daily basis, often revising prior beliefs. Aside from a few cases, such as *BRCA1* and *BRCA2* or the MMR genes, clinicians lack simple and reliable tools to personalize risk prediction, or to help make prevention decisions, for individuals who are found to carry deleterious mutations.

At present, laboratory genetic testing reports include generalized recommendations for management for patients with that particular mutation; however, these recommendations do not necessarily apply to the individual patient. For example, a patient with a *PALB2* mutation, at young age, has about a 45% lifetime risk of developing breast cancer. But that is not true if she is 70 years old, or if she has had risk reducing mastectomies, or if she is 35 and has had her ovaries removed. Gene mutations will have a different significance based on the age of the patient, on the gender of the patient, on whether the patient has had organs removed in the past (e.g., hysterectomy or bilateral mastectomy), and on whether the patient has had cancer in the past (Ma et al. 2017; Mai et al. 2016; Riley et al. 2012). For some genes, it is becoming apparent that risk of disease also varies by the specific pathogenic

variant of a mutation (Cybulski et al. 2007; Thompson et al. 2001). What a provider needs are risk predictions and management options for his or her specific patient.

Effective strategies for prevention or early detection of some cancers (for example, colorectal cancer) are available for high risk individuals, though few are feasible in an untargeted population-wide implementation. An important challenge is to use risk to personalize these prevention strategies. Accurate risk stratification could be used to guide the choice, frequency and age of onset of screening modalities and risk-reducing strategies. For this task, it is important to provide accurate risk stratification for individuals. While studies on gene-cancer associations are growing at a rapid rate, there is no central tool for clinicians to access data from these studies. To address this gap, we developed a systematic approach for (1) data curation, (2) quality assessment, (3) risk estimation, and (4) presentation of risk in an intuitive visualization specific to the patient. The result of this effort is a web-based clinical decision support tool, the All Syndromes Known to Man Evaluator ASK2ME.org.

Materials and Methods

Having identified the need for a tool which provides patient specific risk predictions for all cancer susceptibility genes, we identified the steps needed to create such a clinical decision support tool. These were as follows:

1. Development of a knowledge base structure and maintenance methodology
2. Literature review and data curation into the knowledge base
3. Quality assessment of individual studies
4. Risk estimation
5. Clinician facing interface

Development of a Knowledge Base Structure and Maintenance Methodology

The first component of the infrastructure is the *ask2meKnoweledgeBase* package, written in the object-oriented and open source language R (R Core Team 2017). R is an environment for statistical computing and provides a large variety of statistical and graphical tools. The knowledge base was designed as a set of linked tables that store a machine-readable data set derived from the prose, tables, and figures of published literature regarding gene-cancer associations. We developed tools that facilitated many of the steps required to go from an article in its PDF format to this computable R object. Figure 1 provides an overview of these steps. Brief descriptions of the steps in Fig. 1 will be provided below as we introduce the infrastructure; detailed description of the abbreviations used in Fig. 1 can be found in Supporting Information, Appendix A. At the end of the process, each published study that was identified by search criteria and passed eligibility criteria was embedded in an R object with well-defined fields, which corresponds to *Name.Year.RData* in Fig. 1. These R objects contain prose, tables, or figures of the selected studies named by the first author's last name and the year of publication.

Literature Review and Data Curation into the Knowledge Base

We assembled the relevant studies for each gene-cancer association using well-established systematic review approaches to searching literature databases (Haidich 2010; Khan et al. 2003). We performed PubMed and Embase searches, starting with the following keywords in the title/abstract of the articles: (Gene OR Synonyms) AND (Germline OR Germ-line OR Inherited OR Genetic Predisposition to Disease[MeSH Major Topic]) AND (Penetrance OR Incidence) AND (Cancers of Interest). Here, "Gene" refers to the specific gene considered, for example *APC*. We performed this literature review for all known gene-cancer associations by reviewing associations reported by genetic testing companies as well as those reported by Plichta et al. (2016). We continue to systematically search the literature for studies reporting new associations, as well as update existing ones, so that the knowledge base is dynamic and is updated on an ongoing basis.

Quality Assessment of Each Study

The goal of the quality assessment was (1) to select a single, sufficiently reliable, study to be used for the risk estimation for a specific gene-cancer association or (2) to conclude that no study is of sufficient quality and detail to provide risk estimates. We developed a paper ranking system to assess the quality of published studies for specific gene-cancer associations (Table 1), and, based on this system, which is based on the number of carriers, selected the highest quality study for each gene-cancer association. Unless the selected study is itself a meta-analysis, a major limitation of this approach is that we do not currently integrate information across published studies (this is a future goal, see "Discussion"). We required the highest quality study to have a ranking of three stars or higher. If more than one study had a similar ranking, we chose the study with the larger sampler size. We defined lack of sufficient evidence as being unable to identify studies with a ranking of three stars or higher. In addition, we developed a gene-cancer association ranking (Table 1) to assess the strength of association. This ranking is based on both the number of carriers in the final paper as well as the number of studies on the gene-cancer association in the literature. After studies were ranked based on their quality, appropriate studies were presented and discussed at our combined lab meeting to confirm ratings and clinical utility. The best study was then chosen based on the final ranking, as well as study design and statistical considerations. Recently, Strande et al. (2017) developed a semi-quantitative metric based on ClinGen and the Developmental Disorder Genotype-Phenotype (DDG2P) database which also ranks gene-cancer associations, but differs from our ranking which is based on literature review and the number of carriers in the final paper.

Risk Estimation

After storing data from the best available study for each gene-cancer association in the *ask2meKnowledgeBase* R package, we then estimate the penetrance (e.g., the probability that an individual will develop the disease by a specific age), for each gene-cancer association by gender.

Most studies do not report the penetrance risk estimates directly, but instead report other measures of risk including odd ratios (ORs), hazard ratios (HRs), relative risks (RRs), standardized incidence ratios (SIRs), and cumulative risk (CR) estimates. We developed

statistical methodology to estimate the penetrance from these measures, described in detail in Supporting Information, Appendix B. For studies that do report penetrance estimates directly (cause-specific penetrance, cause-specific survival, or cause-specific cumulative incidence), we are able to use these quantities directly.

For studies reporting one of the following measures: OR, HR, RR, and SIR comparing gene mutation carriers to non-carriers, we assume that the reported ratio is constant throughout the patients' lifetime (unless the study report these quantities stratified by age). In order to estimate penetrance for carriers, we then combine the reported ratio with the baseline risk for noncarriers for each cancer. We obtain this baseline risk estimates from *SEER* (Surveillance, Epidemiology, and End Results Program), which provides the age-specific probability for each cancer by gender through their DevCan software. We obtain data from *SEER 18 Registries*, which we input into their DevCan software and store the output as an R object, *IR.SEER.RData* (Fig. 1).

We incorporated a selected subset of prior cancers and prior surgeries into the risk estimation and into the database. For now, we only adjust for prior cancer by removing the selected cancer when displaying the future risk. This is a very strong assumption, as we assume that (1) prior cancer does not impact the risk of developing other cancers, and (2) prior cancer does not impact the risk of recurrence or second primary cancer (this assumption is discussed further in the "Discussion"). For prior surgeries, we have incorporated mastectomy, oophorectomy, and hysterectomy, all with strong assumptions, that require further extensions (Table 2). We assume hysterectomy reduces the risk of endometrial cancer for carriers and noncarriers of any gene to 0 but has no impact on the risk of other cancers. For oophorectomy and mastectomy, we use established estimates of risk reduction for *BRCA1/2* carriers and noncarriers for breast and ovarian cancers (Katki 2007), and assume that noncarriers and carriers of other genes who have these surgeries have the same risk reduction as the previously estimated reduction for noncarriers.

To fully document the data extraction process, facilitate later modifications, and ensure reproducibility across potentially evolving team membership, we developed R functions specific for each study for a specific gene-cancer association, *GENE_Cancer.R* in Fig. 1. These functions will take in measures of risks reported in the studies stored in *Name.Year.RData* (described earlier), combine these risks with *IR.SEER.RData* if necessary, and finally output the penetrance estimates, stored as *GENE.Cancer.RData* in Fig. 1 (described in detail in the Supporting Information, Appendix C).

Clinician Facing Interface

We created a clinician facing interface (website), which allows users to select gene, gender, age, prior surgery, and prior cancer. After entering this information, the clinician is then provided with patient-specific risk estimates in figures and tables. In addition, next to each figure, we display the citation of the study from which the risk estimates were obtained. For some known gene-cancer associations, there is insufficient data to quantitatively estimate the risk, and these are listed in prose on the output as well.

We developed functions using *GENE.Cancer.RData* stored in the *ask2meKnowledgeBase* R package (Fig. 1) to create a database, which is the back end of the clinician interface website. *genDatabase.R* is created to store the risk estimates for all the gene-cancer associations given on the website, which utilizes *cumRisk.R* function to convert the age-specific risk estimates to age-conditional probabilities of developing cancer. *maxGene.R* is created to provide gene-gender level information displayed on the website, e.g., range for the cancer risk estimates for the same gene and gender, and lack of sufficient evidence for some cancers for a specific gene. *genRef.R* is created to provide gene-gender-cancer level information displayed on the website, e.g., references for each gene-cancer association and the corresponding ratings. More details are provided in the Supporting Information, Appendix C.

Results

The *ASK2ME* website provides patient specific risk estimates by gene-cancer gender for 65 gene-cancer associations (Tables 3 and 4). Please note that the tool is being updated on a monthly basis (details on the exact dates of the updates can be found in the updates log on the *ASK2ME* website), with these tables changing as the tool is updated. The risk for each gene-cancer association is based on extensive literature review identifying reliable studies on the cancer risk implication. For each association, studies are ranked, and risk estimates are based on the highest ranked study (Table 3). For some known associations, we were unable to identify reliable studies for risk estimation, that is we are unable to identify studies with a ranking of three stars or higher based on the ranking system developed (Table 1). These associations are still listed on the website with references.

The website allows users to enter patient-specific characteristics including age, gender, prior cancers, prior surgeries, and gene of interest (Fig. 2). Based on these patient-specific characteristics, the website currently provides patient specific risk estimates in graphs and tables over age, starting at the patient's current age (Fig. 3). Clinicians can look at the patient's risk of cancer at each age for carriers and noncarriers of a specific mutation. For each gene-cancer association, we estimate the penetrance curve for the general carriers of a specific genetic mutation and for the general population. Two penetrance curves are illustrated in Fig. 3, highlighting the implication of prophylactic surgery (in this case mastectomy) on future risk.

In clinical terms, these curves provide absolute risk estimates that are the foundation of decision support. The tool we developed will estimate the penetrance for each of the gene-cancer associations, and tailor it to an individual's age and clinical history. Please note that although not displayed in Fig. 3, our tool displays below each figure the reference and ranking of the study which was used to estimate the figure, allowing clinicians to access those original papers easily.

Discussion

We developed the *ASK2ME* methodology and decision support tool with two goals in mind: (1) to provide an urgently needed systematization of the information used to guide decision

making after panel testing; (2) to lay the foundation for scaling this process as both the number of genes and the relevant papers grows.

Accordingly, the *ASK2ME* website will require continuing updates, and we have designed the infrastructure of the knowledge base to allow for maintenance, enhancements, and extensions. As part of the ongoing work, we are also developing natural language processing algorithms to automate some of the updates and maintenance of the tool. In terms of extensions, the first extension is to other gene-cancer associations. To date, we have covered 29 genes, but other gene associations remain to be included. In addition, as new associations between cancers and genes are discovered, we will undertake a similar literature review, curation, rating, and analysis as described above and update the knowledge base appropriately, as well as conduct updates to current gene-cancer associations. The tool has version control and an updates log, which allows users to keep track of these ongoing updates. In addition, our long-term maintenance plan includes systematic review of each gene-cancer association at least once a year, and the formation of an advisory board to handle contradictory conclusions and ensure that the reviews are complete and upto-date.

We have taken the relatively straightforward approach of assuming that for most genes all pathogenic variants in a given gene will have the same implications on risk. However, it has become apparent that different pathogenic variants of the same gene may have different disease spectra and different penetrance (Groden et al. 1991; Rebbeck et al. 2015). We plan to extend the website to manage variant level risk as well, though this prospect is very challenging. As the list of genes and cancers increases, so will the list of variants, which range from pathogenic or likely pathogenic to variants of unknown significance (VUSs). In order to handle this growing list of variants, we need to devise automated approaches to constantly scan the literature in order to capture these changes.

While we believe that choosing and displaying the results of a single study available of sufficient quality has been a reasonable starting point, we realize that combining multiple studies via a meta-analysis has significant advantages. To this end, we are in the process of conducting a meta-analysis for each gene-cancer association when multiple quality studies are available. When estimating the penetrance using meta-analysis, in addition to taking into account each study's design, there will be additional complexities. Since studies identified in the literature are unlikely to report penetrance directly, and instead report other measures of risk such as OR, HR, RR, SIR, and CR, conducting meta-analysis is not straightforward. Marabelli and co-authors (Marabelli et al. 2016) developed a likelihood-based approach to combine studies reporting penetrance, OR, RR, and SIR, which they apply to estimate the penetrance of breast cancer for *ATM* carriers. We are extending this approach to incorporate, in addition, studies reporting HR and CR.

Estimating the uncertainty of our risk estimates is crucial. One limitation of our tool is that the outputs displayed for clinicians on our website do not currently include confidence intervals for the estimates, though we are currently working on adding the confidence intervals to the plots, and this should be available soon. While we recognize the weaknesses of displaying risk estimates without confidence intervals, clinicians, nurses and genetic counselors are caring for patients with these pathogenic mutations now, and have few tools

to assist them. We are hopeful that in the meantime, even without estimates of uncertainty, presenting a visualization of the best data available can still help clinicians make better decisions. For example, the level of risk for colon cancer with an *APC* mutation compared that of an *MSH2* mutation can help explain why prophylactic surgery may useful for one but not necessary for the other, depending on patient's preferences. While the visualizations we produce may also be used by patients directly, we want to emphasize that *ASK2ME* is designed for clinicians and not as a patient facing site. We can leverage the same knowledge base to produce a patient facing interface after sufficient design and usability analysis, but we have not done so to date.

A next natural step is to validate these risk estimates. Since many of these mutations are less common, a very large database of individuals would need to be collected in order to validate these risk estimates. We are not aware of any large-scale, publicly available cohorts that include panel testing results with the associated clinical information necessary for validation. As panel testing becomes more widely available, we hope that this work will motivate the creation and sharing of such databases.

Another limitation of the *ASK2ME* tool is that it does not yet estimate the risk of a second cancer of a given organ when a prior cancer has occurred. The website does not display future risk for that cancer and assumes that there is no impact on the risk of other cancers. Both of these assumptions may be unrealistic. The risk of second primary cancers can vary dramatically based on the initial treatment of the first cancer (bilateral mastectomy or the use of tamoxifen would both decrease the risk of second primary breast cancers). Also, the treatment of one cancer could potentially decrease the risk of cancers of other organs (ovarian cancer at a young age, treated by oophorectomy, will decrease breast cancer risk). Estimating separate penetrance curves conditional on prior cancer and its treatment will be crucial in estimating accurate risk for a patient (Davies et al. 2015; Trialists' Group 2005).

Extending this tool to provide more accurate and patient-specific risk estimates by allowing users to enter additional characteristics, such as the race of the patient, whether or not the patient is of Ashkenazi Jewish descent, and the specific pathogenic variant is the subject of future work. Adding additional inputs will improve the output of the plots and tables and make the tool more usable in clinical practice, once sufficient data is available and curated.

Incorporating patient-specific management recommendations will enhance the usability of the tool, and we have begun working on this. Providing clinicians with summaries of the current guidelines is a crucial step for increasing the impact of screening and prevention approaches. Clinicians, especially in primary care, are often pressed for time and do not have the resources to keep abreast of current guidelines. The guidelines for clinicians are being updated on a regular basis often changing drastically from 1 year to another. Guidelines can even conflict from one source to another, as sometimes do guidelines from multiple government agencies, insurance companies, professional organizations, and researchers involved in writing guidelines. Our current strategy is to report guidelines from various sources, which currently include (1) National Comprehensive Cancer Network (NCCN), (2) European Society of Medical Oncology (ESMO) Clinical Practice Guidelines for Cancer Prevention and Screening, (3) publication by Tung et al. 2016a, 2016b, and (4)

publication by Graffeo et al. (2016). Note, we do not attempt to assess the quality of these guidelines; rather, we curate the guidelines for clinicians.

Lastly, producing information sheets for patients, letters to referring clinicians, and formatted text to be incorporated in the EHR, will also increase the tool's utility. Clinicians would be able to print these letters and give to them patients, to help guide patients in their decision-making. This feature has the potential of contributing to more uniform and effective communication of results across practitioners and allows patients to understand their results better, share results with family members, and improve disease prevention.

There is growing literature on risk communication and decision support tools. Sim et al. (2001) provide recommendations for clinical decision support systems, and this tool indeed follows some of the recommendations including capturing "literature-based and practice-based evidence in machine-interpretable knowledge bases" and developing "maintainable technical and methodological foundations for computer-based decision support." Shared decision making is becoming a routine component of medical practice, and Hanoch et al. (2015) show that numeracy skills affect a patient's desire to be involved in the decision making process. In addition, Portnoy et al. (2010) study the impact of numeracy skills and health literacy on the ability to learn information during a genetic counseling session and showed that both play an important role of learning information communicated during a session. The decision making process for prophylactic mastectomy among breast cancer patients with no *BRCA* mutations has been studied by Rendle et al. (2015). They identified various factors that influenced this decision making process, including subjective evaluations of risks and benefits. Risk communication is crucial, as numeracy skills of patients can vary dramatically. Studies such as Brewer et al. (2012) have explored the best format to communicate risk for breast cancer recurrence, and we plan to take such studies into account when designing a patient facing interface.

ASK2ME has the potential of having a direct clinical impact by providing a clinical decision support system that allows the clinician to enter the important factors about a patient with a pathogenic variant and immediately receive the risk of various cancers for that mutation for that patient with that current clinical situation. These risk predictions can in turn lead to more personalized prevention and management for individuals undergoing susceptibility testing and potentially help optimize screening and behavioral interventions to reduce risk. Future studies will include quantifying and evaluating the potential impact of the tool.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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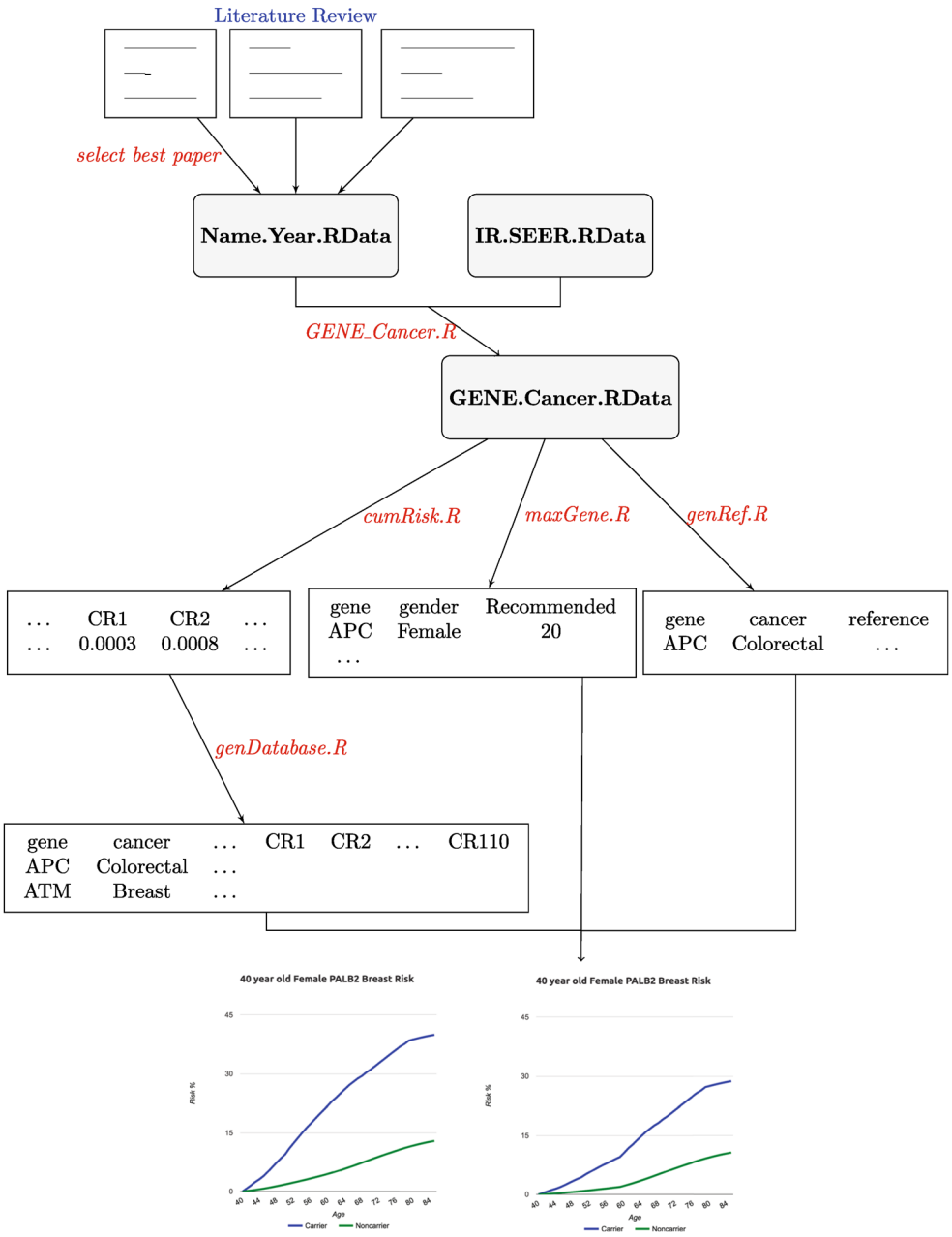

Fig. 1.

Flowchart describing the steps currently used to populate the knowledge base behind the ASK2ME decision support tool

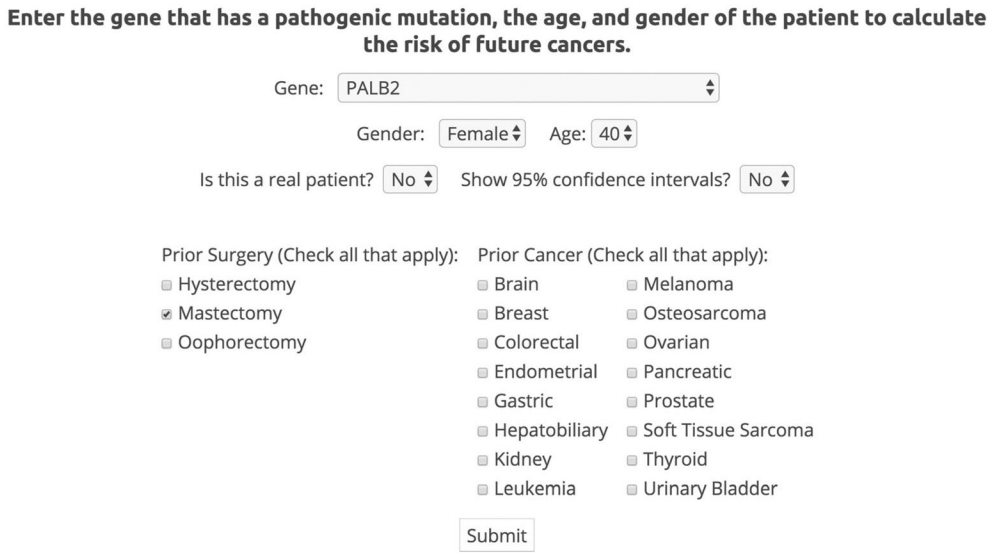

Fig. 2.

ASK2ME user input. The user enters patient information on gene, gender, age, prior surgeries, and prior cancers

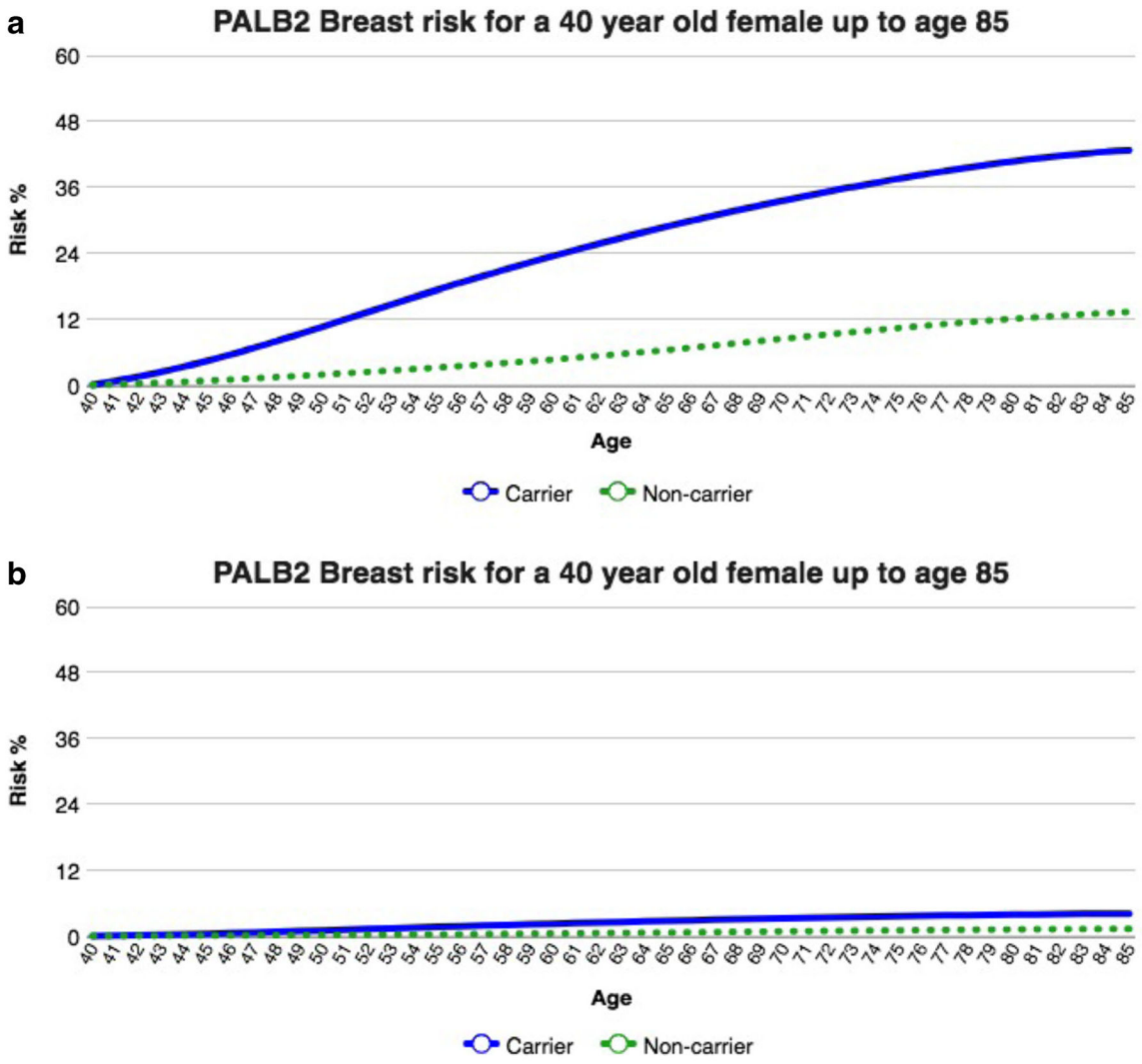

Fig. 3.

Risk of breast cancer for a 40-year-old female carrier of a deleterious germline mutation of the *PALB2* gene, a without mastectomy and b with mastectomy

Table 1

Literature ranking system used to rank studies and associations

Rating	Paper ranking
1	Number of carriers < 50
2	Number of carriers is ≥ 50 and < 100
3	Number of carriers is ≥ 100 and < 200
4	Number of carriers is ≥ 200 and not a meta-analysis
5	Robust meta-analysis
	Gene cancer association ranking
1	Number of carriers in final paper ≤ 50 and number of gene/cancer association studies ≤ 3
2	Number of carriers in final paper ≤ 50 and number of gene/cancer association studies > 3
3	Number of carriers in final paper > 50 and number of gene/cancer association studies ≤ 3
4	Number of carriers in final paper > 50 and number of gene/cancer association studies > 3
5	Meta-analysis

Highest quality study is one with a paper ranking of three or higher. Studies with paper ranking of one or two provide insufficient evidence for risk estimation

Table 2

Risk reduction multiplier for mastectomy, oophorectomy, and hysterectomy, by gender and/or carrier status

	Prior surgery			Carrier status		
	Mastectomy	**Oophorectomy**	**Hysterectomy**	***BRCA1* carriers**	***BRCA2* carriers**	**Noncarriers and other gene mutation carriers**
Female						
Breast cancer	Yes	Yes	–	0.051[1]	0.036[1]	0.046[1]
	Yes	No	–	0.1[2]	0.1[2]	0.1[2]
	No	Yes	–	0.51[3,a]	0.36[3,a]	0.46[a,4]
Ovarian cancer	–	Yes	–	0.31[3]	0.28[3]	0.05[4]
Endometrial cancer	–	–	Yes	0[5]	0[5]	0[5]
Male						
Breast cancer	Yes	–	–	0.1[5]	0.1[5]	0.1[5]

By multiplier, we mean that the risk estimates are multiplied by the factors in this table based on mutation carrier status and the prophylactic surgeries listed in this table

For risk modification for mastectomy for males and hysterectomy for females, risk is modified regardless of carrier status

1. There is not enough information from published papers for these combinations of prior surgeries. Current estimates are obtained by assuming that the joint effect of prophylactic surgeries can be estimated by the product of the effects of individual surgeries

2. We are using the risk reduction rates from conclusions in Rebbeck et al. (2004)

3. We are using the hazard ratios from Domchek et al. (2010). Ratios for oophorectomy and breast cancer are from Table 3; ratios for oophorectomy and ovarian cancer are from Table 2 in the paper

4. We are using the hazard ratios from “Incorporate Oophorectomy into BRCAPRO” section in Katki (2007)

5. There is not enough information from published papers for these combinations of prior surgeries. Current estimates are obtained using clinical subject matter knowledge

a The protective effect of oophorectomy only applies if the patient is under the age of 45

Table 3

References for most reliable literature for associated cancers by gene. Risk estimates in ASK2ME are provided based on the most reliable study for each association

Genes	Cancer	References			
		Female	Paper ranking	Male	Paper ranking
ATM	Breast	Marabelli et al. (2016)	5	–	
	Colorectal, gastric, pancreatic, prostate	Helgason et al. (2015)	4	Helgason et al. (2015)	4
BRCA1	Breast (F), ovarian	Chen and Parmigiani (2007)	4	Chen and Parmigiani (2007)	4
	Pancreatic	Mocci et al. (2013)	4	Mocci et al. (2013)	4
BRCA2	Breast, ovarian, prostate	Chen and Parmigiani (2007)	5	Roed Nielsen et al. (2016)	3
	Pancreatic	Mocci et al. (2013)	4	Mocci et al. (2013)	4
BRIP1	Ovarian	Ramus et al. (2015)	3	–	
CDH1	Breast (F), gastric	Hansford et al. (2015)	3	Hansford et al. (2015)	3
CDK4	Melanoma	de Snoo et al. (2008)	3	de Snoo et al. (2008)	3
CDKN2A/p16	Melanoma, pancreatic	de Snoo et al. (2008)	3	de Snoo et al. (2008)	3
CHEK2/1100delC	Breast	Schmidt et al. (2016)	5	–	
	Colorectal	Ma et al. (2013)	5	Ma et al. (2013)	5
	Prostate	–		Wang et al. (2015)	5
MLH1	Colorectal, gastric	Dowty et al. (2013)	4	Dowty et al. (2013)	4
	Ovarian	Engel et al. (2012)	4	–	
MSH2	Colorectal, endometrial, gastric (F), pancreatic	Dowty et al. (2013)	4	Dowty et al. (2013)	4
	Ovarian	Engel et al. (2012)	4	–	
MSH6	Colorectal, endometrial	Bonadona et al. (2011)	4	Bonadona et al. (2011)	4
	Gastric	Barrow et al. (2009)	3	Barrow et al. (2009)	3
	Ovarian	Engel et al. (2012)	4	–	
MUTYH-Biallelic/G396D	Colorectal	Theodoratou et al. (2010)	5	Theodoratou et al. (2010)	5
MUTYH-Biallelic/Compound Heterozygous	Colorectal	Theodoratou et al. (2010)	5	Theodoratou et al. (2010)	5
MUTYH-Biallelic	Ovarian, urinary bladder	Win et al. (2016)	3	–	
MUTYH-Monoallelic	Colorectal, endometrial, gastric, hepatobiliary	Win et al. (2016)	3	Win et al. (2016)	3
NBN/657del5	Breast	Zhang et al. (2012)	3	–	
	Prostate	–		Cybulski et al. (2013)	3

Genes	Cancer	References			
		Female	Paper ranking	Male	Paper ranking
PALB2	Breast	Antoniou et al. (2014)	4	–	
	Pancreatic	Mocci et al. (2013)	4	Mocci et al. (2013)	4
PMS2	Colorectal, endometrial	Ten Broeke et al. (2014)	4	Ten Broeke et al. (2014)	4
	Ovarian	Engel et al. (2012)	4	–	
PTEN	Breast(F), colorectal, endometrial, kidney, melanoma, thyroid	Engel et al. (2012)	4	Tan et al. (2012)	4
RAD51C	Ovarian	Song et al. (2015)	4	–	
RAD51D	Ovarian	Song et al. (2015)	4	–	
STK11	Breast (F), colorectal, pancreatic	Resta et al. (2013)	3	Resta et al. (2013)	3
	Gastric	Van Lier et al. (2010)	5	Van Lier et al. (2010)	5
TP53	Breast(F), brain, leukemia, osteosarcoma, soft tissue	Mai et al. (2016)	4	Mai et al. (2016)	4

Table 4

Gene cancer associations currently included in ASK2ME

Genes	Reliable studies for risk estimation	
	Yes	**No**
ATM	Breast (F), colorectal (F/M), gastric (F/M), pancreatic (F/M), prostate	Breast (M), leukemia (F/M), lymphoma (F/M)
BMPR1A	–	Colorectal (F/M), gastric (F/M), pancreatic (F/M), small bowel (F/M)
BRCA1	Breast (F/M), ovarian, pancreatic (F/M)	Fallopian tube, peritoneal, prostate
BRCA2	Breast (F/M), ovarian, pancreatic (F/M), prostate	Fallopian tube, peritoneal, melanoma (F/M)
BRIP1	Ovarian	Breast (F)
CDH1	Breast (F), gastric (F/M)	Colorectal (F/M)
CDK4	Melanoma (F/M)	Pancreatic (F/M)
CDKN2A/p16	Melanoma (F/M), pancreatic (F/M)	Melanoma (F/M), pancreatic (F/M)
CDKN2A/p14	–	Melanoma (F/M), pancreatic (F/M)
CHEK2/1100delC	Breast (F), colorectal (F/M), prostate	Thyroid (F/M), ovarian, kidney (F/M)
GREM1	–	Colorectal (F/M)
MLH1	Colorectal (F/M), endometrial, gastric (F/M), ovarian	CNS (F/M), hepatobiliary (F/M), kidney (F/M), pancreatic (F/M), prostate Sebaceous gland (F/M), skin (F/M), small bowel (F/M), ureter (F/M), urinary bladder (F/M)
MSH2	Colorectal (F/M), endometrial, gastric(F), ovarian, pancreatic (F/M)	CNS (F/M), gastric (M), hepatobiliary (F/M), kidney (F/M), pancreatic (F/M), prostate Sebaceous gland (F/M), small bowel (F/M), ureter (F/M), urinary bladder (F/M)
MSH6	Colorectal (F/M), endometrial, gastric (F/M), ovarian	CNS (F/M), hepatobiliary (F/M), kidney (F/M), pancreatic (F/M), prostate Sebaceous gland (F/M), small bowel (F/M), ureter (F/M), urinary bladder (F/M)
MUTYH-Biallelic/G396D	Colorectal (F/M)	–
MUTYH-Biallelic/CH	Colorectal (F/M)	–
MUTYH-Biallelic	Ovarian, urinary bladder (F/M)	Breast (F), small bowel (F/M)
MUTYH-Monoallelic	Colorectal (F/M), endometrial, gastric (F/M), hepatobiliary (F/M)	Breast (F), small bowel (F/M)
NBN/657del5	Breast (F), prostate	Ovarian, skin (F/M)
PALB2	Breast (F), prostate, pancreatic (F/M)	Breast (M)
PMS2	Colorectal (F/M), endometrial, ovarian	CNS (F/M), gastric (M), hepatobiliary (F/M), kidney (F/M), pancreatic (F/M), prostate Sebaceous gland (F/M), small bowel (F/M), ureter (F/M), urinary bladder (F/M)
POLD1	–	Colorectal (F/M)
POLE	–	Colorectal (F/M)

Genes	Reliable studies for risk estimation	
	Yes	**No**
PTEN	Breast (F), colorectal (F/M), endometrial, kidney (F/M), melanoma (F/M), thyroid (F/M)	Urinary bladder (F/M)
RAD51C	Ovarian	Breast (F)
RAD51D	Ovarian	Breast (F)
SMAD4	–	Colorectal (F/M), gastric (F/M), pancreatic (F/M), small bowel (F/M)
STK11	Breast (F), colorectal (F/M), gastric (F/M), pancreatic (F/M)	Lung (F/M), endometrial, ovarian, small bowel (F/M)
TP53	Breast (F), brain (F/M), leukemia (F/M), osteosarcoma (F/M), soft tissue (F/M)	Lung (F/M), endometrial, gastric (F/M), melanoma (F/M), ovarian, prostate

Penetrance estimates are provided for associations for which quality of studies was high enough to estimate risk. A list of cancer associated with a specific gene, for which there is not enough evidence to estimate risk is also provided

CNS central nervous system, *MUTYH-Biallelic/CHMUTYH*-biallelic/compound heterozygous