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Authors

Nerb, Laura

Yang, Emily

Exume, Dominique

et al.

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Development, Usability Testing, and Implementation Assessment of Cancer Related Infertility Score Predictor, an Online Cancer Related Infertility Risk Counseling Tool

Laura Nerb, BS,¹ Emily Yang, BS,¹ Dominique Exume, MD,² Anna Dornisch, MD, MAS,³ Beth Zhou, MD,⁴ Teresa Helsten, MD,⁵ Bonnie N. Kaiser, PhD,⁶ Sally A.D. Romero, PhD, MPH,⁴ and H. Irene Su, MD, MSCE^{4,5}

Purpose: Oncofertility counseling of female cancer patients lacks efficient access to tailored and valid infertility risk estimates to support shared decision-making on fertility preservation treatments. The objective was to develop, conduct user-centered design, and plan clinic-based implementation of the Cancer Related Infertility Score Predictor (CRISP), a web-based tool to support infertility risk counseling.

Methods: Using a mixed methods design, literature review was undertaken to abstract data on infertility, primary ovarian insufficiency, and amenorrhea risks of common cancer treatments. The CRISP website was programmed to take user input about patient ages and cancer treatments and generate a risk summary. Using user experience methodology and semistructured interviews, usability testing and implementation assessment were conducted with 12 providers recruited from 5 medical centers in Southern California.

Results: The web-based CRISP tool encompasses infertility risk data for 60 treatment regimens among 10 cancer types. Usability testing demonstrated that the tool is intuitive and informed minor modifications, including adding crowd-sourced submission of additional cancer treatments. Participants rated the tool as credible, advantageous over current provider methods to ascertain infertility risks, and useful for tailoring treatment planning and counseling patients. A key barrier was lack of information on some cancer treatments. Fit within clinical workflow was feasible, particularly with electronic health record integration.

Conclusions: The novel, web-based CRISP tool is a feasible, acceptable, and appropriate tool to address provider knowledge gap about cancer related infertility risks and use for patient counseling. CRISP has significant potential to support tailored oncofertility counseling in the heterogeneous young cancer patient population.

Keywords: oncofertility, fertility preservation, cancer infertility, primary ovarian insufficiency, amenorrhea, infertility risk tool

Introduction

FEMALE CANCER SURVIVORS diagnosed as children, adolescents, and young adults are at an increased risk of infertility and premature ovarian insufficiency (POI) compared to women without cancer.¹⁻³ Because fertility preser-

vation strategies are effective in decreasing infertility and POI risks, oncofertility counseling on reproductive risks and fertility preservation strategies is recommended by clinical oncology and reproductive medicine societies to improve survivorship outcomes.⁴⁻⁶ Yet, nearly half of female cancer patients in the United States still do not receive counseling,⁷

¹School of Medicine, University of California San Diego, La Jolla, California, USA.

²Department of Obstetrics and Gynecology, Penn State Hershey Medical Center, Hershey, Pennsylvania, USA.

³Department of Radiation Medicine and Applied Sciences, University of California San Diego, La Jolla, California, USA.

⁴Department of Obstetrics, Gynecology and Reproductive Sciences, University of California San Diego, La Jolla, California, USA.

⁵Moore's Cancer Center, University of California San Diego, La Jolla, California, USA.

⁶Department of Anthropology and Global Health Program, University of California San Diego, La Jolla, California, USA.

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which contributes to lowered post-treatment quality of life and emotional distress in many of the >400,000 U.S. female cancer survivors younger than 40 years of age.^{8–10}

Absence of pathways for referral, limited availability of providers, high cost, and limited health literacy represent barriers to patients accessing this care.¹¹ Furthermore, as infertility risks differ by cancer treatments,¹ cancer survivors as well as oncology and fertility health care providers need information on treatment-specific infertility risks to support shared decision-making on fertility preservation. However, both cancer survivors and health care providers report knowledge gaps on infertility risks of cancer treatments, which contribute to disparities in care due to variable quality of oncofertility counseling, including omission of risk information.^{12–14}

Currently, estimating infertility risk relies on provider knowledge or review of published primary data and expert opinions, which is time-consuming and inefficient, especially during clinic visits.^{15,16} Thus, there is an unmet need for a tool that quickly and accurately summarizes infertility risks to support oncofertility counseling and shared decision-making. Such a tool could also function as a stopgap in addressing the disparities in provision of prompt, affordable, and easily understood oncofertility counseling. Web-based risk tools are already used for clinical decision support for estimating breast cancer risk and long-term survival.^{17–20} Clinical decision support tools increase adherence to clinical guidelines, improve quality of clinical documentation, and aid in shared-decision making by providing patients with more data and the means to participate in informed choices.²¹ Current online infertility risk tools are limited by broad risk groupings,^{22,23} focus on childhood cancer only,²⁴ and/or lack of field testing.

The study goal was to develop and evaluate a web-based infertility risk summary tool, the Cancer Related Infertility Score Predictor (CRISP). Guided by the Consolidated Framework for Implementation Research (CFIR), our objectives were to conduct usability testing of the intervention and qualitatively assess intervention fit with oncofertility counseling in adult and children's oncology and fertility settings.^{25,26}

Materials and Methods

A mixed-methods study was undertaken following approval by the Institutional Review Board at the University of California, San Diego.

Tool development

Derivation of cancer treatment-related infertility risks. We previously conducted a prospective population-based cohort study on the impact of cancer treatments on ovarian function in 763 female adolescent and young adult (AYA) cancer survivors.²⁷ The most common individual drug, chemotherapy regimen, radiation, and surgery exposures from this prior study were used to inform our targeted review of their impact on risks of infertility, acute ovarian failure, POI, as well as on surrogate outcomes of ovarian reserve tests and amenorrhea.

We searched PubMed (Supplementary Data S1), Web of Science, Embase, and Food and Drug Administration (FDA) package inserts to obtain primary outcome data from ran-

domized controlled trials and cohort studies and searched reference lists of all included studies for additional relevant sources. Two clinician investigators reviewed the data and came to a consensus on estimated absolute and relative risks of outcomes stratified by age at treatment, hierarchically prioritizing outcomes in the following order: infertility, live births, acute ovarian failure, POI, decreased ovarian reserve, and amenorrhea. Where studies reported varied, we hierarchically prioritized by rigor of study design and sample size.

Programming CRISP. CRISP was programmed by researcher (L.N.) using HTML, CSS, and JavaScript. The program takes user input about a patient's age and cancer treatment regimen, and outputs an infertility risk summary that can be saved as pdf or printed. The risk summary includes patient name (optional), patient age, a color-coded infertility risk estimate (low-green, moderate-yellow, high-red, or unknown-black) that is accompanied by a risk percentage, which clinical outcome (“amenorrhea” vs. “acute ovarian failure” vs. “infertility” vs. “premature menopause”) is describe by the risk estimate, comparison risks in women without cancer,²⁸ a list of relevant references, American Society of Clinical Oncology (ASCO) clinical guidelines, and date of output. Treatment exposures designated as unknown indicate literature review revealed no credible estimate.

In contrast, if the CRISP search yields treatment exposures that are not found, the output is a prompt to submit a request to the research team. A further feature is the addition of a cyclophosphamide equivalent dosing (CED) calculator.²⁹ Because infertility risk evidence will change over time, the website supports crowdsourcing of new regimens of interest; crowd-sourced infertility data and references will be verified by the investigator team before being added to the database.

Depiction of risks. The goal of the risk summary is to increase patient and provider understanding of cancer treatment-related infertility risks (Fig. 1).³⁰ We selected icon arrays and part-to-whole relationships, because health risk communication data suggest people understand better with this format than with percentages or proportions.³¹ We reduced the presentation to a denominator of 10, indicated by the number of filled circles out of a total of 10, and also presented risk as low ($\leq 20\%$), moderate (21%–70%), or high ($>70\%$), which may be preferred by women and individuals with less health literacy.³²

We selected $<20\%$ as low risk, as infertility risk in the general population is 10%–20%.²⁸ The threshold between moderate and high was selected by the clinician research team. We used circles in the array instead of female or mixed gender stick figures based on preferences of female AYA cancer survivors, some of whom may prefer this representation, given their gender identity or gender expression.

Usability testing and implementation assessment

Participant recruitment. Between June and September 2020, a purposive sample of oncology and fertility physicians, advanced practice providers, and social workers was recruited by email from five medical centers in Southern California to participate in semistructured interviews focused on evaluating CRISP usability and how CRISP would fit into their clinical practice. Participating sites included University

The image shows two parts of the CRISP website. On the left is the home page with a navigation bar (CRISP Home, CED Calculator, Who We Are, Contact Us) and a logo for 'Reproductive Care'. The main heading is 'Cancer Related Infertility Score Predictor'. A text box explains that CRISP calculates population-based infertility risk based on age, cancer treatment, and current data, but notes that the website is currently under construction and not for use yet. Below this is a form with fields for Patient Name, Age, Cancer Type, and Exposure Type, along with a 'Reset' button and a 'Continue' button. On the right is a 'Reproductive Risk Summary' for Jane Doe, age 30, with Breast cancer. It shows an 'Estimated Infertility Risk is MODERATE' with a visual scale of 10 circles (5 filled, 5 empty). It compares this to a 1% risk of primary ovarian insufficiency in young women without cancer. It lists the treatment as CEF (Cyclophosphamide, Epirubicin, Fluorouracil) with a 41-50% risk of Amenorrhea (12 months). A legend indicates Low risk (green), Moderate risk (yellow), High risk (red), and No clinical data (black). It also includes ASCO clinical guidelines, the date prepared (4/6/2023), and a reference to Parulekar et al. (2005).

FIG. 1. Left: CRISP home page takes user input about patient name (optional), age, cancer type, and exposure type. Not pictured, these inputs then generate tailored exposure options for the user to choose from (i.e., specific chemotherapy regimens or radiation doses). Right: Sample Reproductive Risk Summary includes patient name (Jane Doe), age (30), color-coded infertility risk estimate (yellow-moderate), risk percentage and associated clinical outcome (41%–50% risk of Amenorrhea-12 months), comparison risk in women without cancer, ASCO clinical guidelines, date of output, and a list of references. ASCO, American Society of Clinical Oncology; CRISP, Cancer Related Infertility Score Predictor.

of California San Diego, Children’s Hospital of Orange County, City of Hope, Cedars Sinai, and University of Southern California. Saturation is the point at which additional data collection does not yield new insights and is the gold standard for stopping recruitment.³³ Recruitment was stopped when data saturation on content representation, workflow issues, and CFIR constructs was achieved. All participants granted informed consent, no participant declined to participate or dropped out, and no repeat interview was conducted. Participants were aware of researchers’ goals for the study and interests in the research topic.

Content representation and technical/workflow issues were addressed with a human-centered design approach.³⁴ Following a think-aloud protocol,^{34–36} two researchers (L.N., H.I.S., and/or E.Y.) asked users to verbalize their thought processes as they completed study tasks with the risk tool. Navigating website, correctly selecting input values, and accurately interpreting risk summaries were benchmarks for success. Intervention appropriateness for that stakeholder’s context was assessed qualitatively by asking questions such as “does this tool seem helpful?” or “why/why not would you use this tool?”

Intervention feasibility was assessed by asking questions such as “are input fields simple to understand?” or “what type of training if any would be needed to learn how to use CRISP?” After observing users interacting with CRISP, re-

searchers conducted virtual interviews lasting 15–30 minutes. A CFIR-guided interview guide was used to assess multilevel factors that could impact CRISP intervention implementation, focusing on the domains of intervention characteristics (e.g., evidence strength and quality, relative advantage, complexity, design quality and packaging), inner setting of clinical care settings (e.g., implementation climate), and characteristics of individuals (e.g., knowledge and beliefs).²⁵ Audio recording and note-taking occurred during usability testing and interviews.

Data analysis

Thematic content analysis was facilitated by MaxQDA software.³⁷ In addition to deductive themes (e.g., CFIR constructs^{25,26}), inductive themes arising from the data were identified using the following steps: (1) two independent coders (L.N. and E.Y.) read the transcripts, becoming familiar with the text and developing initial codes by consensus, (2) the same two coders coded three transcripts iteratively and refined the codebook, and (3) the final codebook was determined by consensus (L.N., E.Y., and H.I.S.).

Inductive and deductive codes were applied to all transcripts using consensus coding (two coders independently coded each transcript and resolved discrepancies by consensus). Code summaries were developed, which described

the breadth and depth of each code, and final themes and subthemes were developed to create a cohesive message. These steps ensured that all transcripts were coded by two researchers, maintaining rigor and reliability throughout the coding process. Participants did not provide feedback on findings and transcripts were not returned to participants for comment.

Results

CRISP is a web-based tool that provides population-based infertility risks based on patient age at treatment and type of cancer treatment, using fertility and ovarian function outcome data obtained from literature reviews (Fig. 1). Risk data are available for over 60 treatments among 10 different cancer types (brain, breast, cervical, Hodgkin's lymphoma, intestinal, leukemia, Non-Hodgkin lymphoma, ovarian, sarcoma, and uterine). Usability testing and interviews were conducted with nine oncology and three fertility clinicians (eight physicians, three advanced practice providers, and one social worker); 7 of 12 participants were female.

Usability testing

CRISP design, content, and workflow issues and resultant modifications are summarized in Table 1. Most users reported navigating the tool to be "user-friendly" and "intuitive." Visual representation of risks through graphic and red/yellow/green color scheme was frequently endorsed: "I really like these dots. I think that helps patients visualize this really well" (Oncologist 1). The inclusion of risks in women without cancer for comparison was frequently cited as helpful. Users had difficulty recognizing required (e.g., age) versus optional (e.g., patient name to allow personalization of results) input fields, with some providers uncomfortable with entering patient names. Users wished to compare the risks of multiple potential treatments and found the method of resetting the planned treatment nonintuitive: "Let's say I change my mind. And I don't want to do chemotherapy, I want something else. [How do I] go...back?" (Oncologist 2).

Facilitators and barriers of CRISP implementation in clinical care

Intervention characteristics. Several themes emerged on evidence strength and quality, relative advantage, and complexity (Table 2). A majority of providers rated CRISP as a credible resource due to citation of peer-reviewed articles and development by an academic oncofertility team. Multiple providers noted frustration from missing treatment regimens or unknown risks due to a lack of published data. Providers endorsed the concept of crowdsourcing through the embedded online form to request the addition of missing regimens. Several reproductive specialists expressed that, while helpful for patient education, the output may be oversimplified and would benefit from provider interpretation and citation of multiple references per treatment. For example, "we know that the risk of amenorrhea is not equivalent to the risk of infertility. And so I think that that's something we have to be very careful about" (Fertility Specialist 1).

Compared to current strategies of recalled knowledge, primary literature searches, or relying on Children's Oncology Group (COG) protocols, providers noted several relative advantages of CRISP: time savings, availability of data on multiple treatments for risk comparison, validation of existing knowledge, and facilitating calculation of CED. For example, "I think [CRISP] would be helpful because it quantifies [fertility risk] more. Rather than me thinking okay, based on this literature ...[now] you don't have to look it up every single time" (Oncologist 3). Furthermore, CRISP facilitates patient-provider communication by providing a quantified risk estimate that is simpler than showing complex graphs from primary studies.

On the complexity of implementing CRISP, providers did not feel training on how to use the intervention was needed because use is intuitive: "I think it's something that can be readily adopted into clinical practice... Just remembering the website name [will be a barrier]" (Oncologist 4). Several suggestions for implementation arose, including integration into the electronic health record (EHR) system, for example, embedding in clinical decision tools or SmartPhrases in the EPIC EHR (four of five medical centers in this study use EPIC), saving the link as a web browser bookmark on clinic

TABLE 1. CANCER RELATED INFERTILITY SCORE PREDICTOR DESIGN AND WORKFLOW ISSUES IDENTIFIED IN USABILITY TESTING AND CORRESPONDING MODIFICATIONS

<i>Usability issue</i>	<i>Solution</i>
Users desired to change input (cancer treatment) after viewing initial risk summary	Added "Reset" button
Users did not recognize which fields were required vs. optional	Marked required fields with an asterisk
Users wanted more cancer treatments than had been summarized	Included link to form where users can request additional specific treatments. Emphasized link through warning graphic
Users requested output to include clinical guidelines	Added ASCO clinical guidelines to output
Users thought having multiple graphics in output was confusing	Condensed information into a single graphic
Users wanted more information about how CRISP calculates risk	Explained how risk is calculated in the "Who We Are" section of the website
Users wanted the ability to calculate the CED	Added CED calculator

TABLE 2. FACILITATORS (WHITE BOXES) AND BARRIERS (GRAY BOXES) TO CANCER RELATED INFERTILITY SCORE PREDICTOR IMPLEMENTATION CATEGORIZED BY CONSOLIDATED FRAMEWORK FOR IMPLEMENTATION RESEARCH CONSTRUCTS AND POTENTIAL IMPLEMENTATION STRATEGIES

<i>CFIR construct</i>	<i>Barriers (gray boxes) and facilitators (white boxes)</i>
Intervention characteristics	
Evidence strength and quality	<p>Credibility from citation of peer-reviewed references</p> <p>Credibility due to development by a reputable source</p> <p>Unknown infertility risk output due to lack of primary data. <i>Solution: continue to update website as new data become available</i></p> <p>Treatment regimens missing from the website. <i>Solution: crowdsourcing</i></p> <p>Single reference citations oversimplify existing data. <i>Solution: add more citations to website</i></p> <p>Outcomes represented (e.g., amenorrhea vs. infertility risk) would benefit from additional specialist interpretation. <i>Solution: CRISP should be used in consultation with medical professionals.</i></p>
Relative advantage	<p>Time savings from primary literature search</p> <p>Validation of provider knowledge</p> <p>Data on multiple regimens allow risk comparison</p> <p>For patients: information more reliable than Internet search, which simplifies decision on whether to pursue fertility preservation</p> <p>Quantification of risk on web-based interface facilitates patient-provider communication</p> <p>Facilitates calculation of CED</p>
Design quality and packaging	<p>Intuitive to use</p> <p>Simple graphics with easy to follow red/yellow/green color schema</p> <p>Quantifies risk and compares risk to general population</p> <p>Printable output provides materials that reinforce discussion after office visit</p>
Complexity	<p>No provider training on CRISP tool use needed</p> <p>Recalling intervention’s website location. <i>Solution: integrate link into EHR clinical decision support, make dot phrase, save link to bookmarks, physical reminder cards</i></p>
Adaptability	<p>Tool is desktop and mobile friendly</p>
Inner setting	
Implementation climate: compatibility	<p>Compatible with different workflows: useful while pre-charting and/or during patient consult, can be provided as a take-home handout, can be part of oncofertility risk discussion documentation</p> <p>Concern that documentation of low risk depiction may limit insurance coverage. <i>Solution: CRISP should be used in consultation with medical professionals, who can interpret risk and indicate medical necessity of fertility preservation services.</i></p> <p>Intervention and output are not embedded in EHR. <i>Future goal</i></p>
Characteristics of individuals	
Self-efficacy	<p>Providers feel capable of sharing risk data with patients</p> <p>Providers may believe oncofertility risk discussion is beyond their scope of work. <i>Solution: develop additional provider education, disseminate clinical guideline recommendations for oncofertility care, mandate change</i></p>
Knowledge and beliefs	<p>Useful for provider education and behavior: fills in knowledge gaps, guides treatment planning decisions, compels providers to conduct fertility risk counseling and refer to fertility specialists</p> <p>Uptake of tool will vary by motivation of providers to engage in oncofertility care. <i>Solution: mandate change</i></p>

Solutions for barriers in italicized text.

CFIR, Consolidated Framework for Implementation Research; EHR, electronic health record.

computers, memorizing the website from frequent use, or placing laminated tip sheets in clinic.

Inner setting. Within clinic settings in which CRISP would be implemented, we assessed the intervention’s compatibility with existing workflows. Some providers said they would use the tool during pre-charting for planning the oncofertility discussion. This would enable them to determine “what my anticipated plan would be before I see [the patient]” (Oncologist 1). Multiple oncology providers an-

icipated showing the output to the patient during the consultation and providing the output as a handout: “I think it’s really helpful as a patient handout... When [patients] come in to... talk about cancer for the first time...they don’t remember anything. So picking out printouts and things like that, that can be helpful” (Oncologist 3).

A major barrier to compatibility was that the intervention is outside of the EHR. Providers desired CRISP output to be directly documented in patients’ charts, to alleviate future need to recalculate risks and communicate among providers.

Individual characteristics. The majority of providers reported motivation to use CRISP to improve their knowledge, facilitate oncofertility discussions, and factor risk output into cancer treatment planning: “That’s good to know this is what their risk of infertility is, and I’m really going to have to plan into their chemo regimen potentially egg retrieval or Zoladex injection” (Oncologist 1). A driving factor was that more specific risk data are clinically useful for treatment planning: “It simplifies risk stratification, right? Because you’re already telling me, there’s a moderate risk. So that tells me I really need to address fertility... if it’s low, it will guide me to say, okay, you know, we should just really get going [with cancer treatment]” (Oncologist 5).

Providers expressed the belief that uptake will vary by provider’s interest in oncofertility. “I suppose [uptake of tool is] based on the motivation of the provider... That’s going to be different based on how interested in fertility concerns the provider may be” (Oncologist 1). One provider reported that they would not use CRISP because oncofertility counseling is beyond their scope of work; providing these risk estimates may lead to follow-up questions that the provider could not answer. “Fertility is not our specialty here. So if they start asking questions, [I say] you’re just gonna have to meet [the fertility specialist]. And she can answer your questions” (Oncology Advanced Practice Provider 1).

Discussion

Oncofertility counseling of female cancer patients lacks efficient access to reliable and valid reproductive risk estimates to aid in shared decision-making on fertility preservation treatments.^{15,38,39} To this end, we developed CRISP, a tool that has significant potential to support tailored cancer treatment-related infertility risk counseling in the heterogeneous young cancer patient population by addressing the provider knowledge gap about infertility risks and simplifying reproductive health information that providers can share with patients. We also identified barriers to CRISP implementation, such as lack of risk information for some cancer treatments and the need for provider interpretation of data with patients.

Unlike most existing oncofertility decision-making aids that target patients, CRISP aims to support providers, who can tailor risk counseling based on cancer type.¹⁸ Other benefits include risk depiction with quantitative scores rather than more generalized groupings²³ and applicability to multiple age groups rather than children alone.²⁴ Importantly, the age at treatment and cancer treatment regimens are the two known risk factors for infertility after cancer, and both are incorporated into the tool. Consequently, participants reported that CRISP will be useful in their clinic practice by supporting tailoring treatment planning, counseling patients, and providing patients with written estimates.

Importantly, participants noted that CRISP is not intended as a stand-alone decision aid as interpretation of reproductive outcomes is needed to discuss nuances regarding fertility risk, especially for patients who have low health literacy.⁴⁰ Furthermore, decision aids are not meant to substitute for clinical care¹⁸; instead, provider-guided interpretation of CRISP output is intended to facilitate a more in-depth discussion of cancer treatment-related infertility risks, fertility preservation options and referral to fertility specialists. In

addition, existing resources that include features such as video testimonials and detailed fertility preservation options^{41,42} can be used in conjunction with our tool to enhance overall patient education and clinical decision-making. CRISP can also be used alongside fertility preservation scripts.⁴³

Published risk stratification tools include those of The Pediatric Initiative Network Risk Stratification System of the Oncofertility Consortium,¹⁵ the Childhood Cancer Survivor Study,¹⁶ the COG,⁴⁴ and the International Late Effects of Childhood Cancer Guideline Harmonization Group.⁴⁵ CRISP aligns with these tools in that alkylating agents (by cumulative dose and age at exposure), pelvic radiation, and CNS radiation yield increased reproductive risks. CRISP is distinct from these tools as specific rates (e.g., 11%–20%) and outcomes (e.g., amenorrhea, infertility) are provided; these data are by regimen rather than class of exposure; and/or data for regimens that do not contain alkylators, radiation, and/or heavy metals are included.

On clinic-based implementation, CRISP was deemed simple and intuitive to use, so implementation strategies will not include additional training and will instead focus on fit into clinical workflows and dissemination. This can be achieved by conducting educational meetings with oncology and fertility providers, informing local opinion leaders, mandating change, and then subsequently reminding clinicians (which can be facilitated by incorporating CRISP into EHR clinical decision support).⁴⁶ We also plan to address FAQs submitted to investigators directly on the CRISP website, in a separate tab accessible through the navigation menu.

Although CRISP was overall favorably received by providers, there are still some tool limitations. Because CRISP only calculates infertility risk for cancer treatments with data that were abstracted from a literature review by the investigator team, CRISP cannot calculate risk for all cancer treatments. Thus, we have added a crowd sourcing feature to the website, where users can submit missing treatment alerts and references to our team. We will also continue to update CRISP as new risk data become available and in response to crowd-sourced questions on missing regimens. Despite this solution, many treatment risks will remain “unknown” due to lack of primary data. Selection bias may impact generalizability, given that providers were recruited through convenience purposive sampling from sites in Southern California, and some had previously collaborated with our team and had preexisting interest in fertility or pediatric, adolescent, or young adult cancer survivorship care.

The participant pool was also predominantly academic, so future work is needed to learn if results are generalizable to additional populations such as community oncologists. Another limitation is that CRISP has not yet been directly integrated into an EHR due to lengthy approval processes, programming requirements, and the variety of EHR systems. Currently, CRISP is housed at an intuitive domain name www.oncofertilityrisk.com, and providers must rely on bookmarks, dot phrases, or reminder cards to access the website link. Future implementation will require further studies to examine efficacy and implementation outcomes.

In summary, we developed CRISP, a novel, web-based counseling tool that facilitates fertility risk discussions between providers and cancer patients, thus allowing patients to make more informed decisions regarding whether to pursue fertility preservation treatments. Furthermore, we identified

potential facilitators and barriers to CRISP implementation and have plans to address them, which will expedite integration of the intervention into clinical care.

Authors' Contributions

Conception or design of the work (L.N., A.D., S.A.D.R., and H.I.S.). Acquisition, analysis, or interpretation of data for the work (all authors). Drafting the work or revising it critically for important intellectual content (all authors). Final approval of the version to be published (all authors).

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Author Disclosure Statement

No competing financial interests exist.

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Supplementary Material

Supplementary Data

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Address correspondence to:

H. Irene Su, MD, MSCE

*Department of Obstetrics, Gynecology
and Reproductive Sciences*

*University of California San Diego
3855 Health Sciences Drive, MC 0901
La Jolla, CA 92093-0901*

USA

Email: hisu@health.ucsd.edu