INTRODUCTION

There currently exist a large number of US clinics offering stem-cell-based interventions (SCBIs) for many different medical conditions. Researchers have been tracking this marketplace, publishing studies that characterize these clinics and their care providers (Frow et al., 2019; Fu et al., 2019; Knoepfler and Turner, 2018; Turner, 2018; Turner and Knoepfler, 2016). Scientific and bioethical communities continue to call for stronger regulation and oversight of this sector, emphasizing the “unproven” nature of the SCBIs routinely on offer and highlighting the lack of evidence demonstrating their clinical efficacy (ISSCR, 2015; Sipp et al., 2017; Zarzeczny et al., 2018). Yet the marketplace remains strong, suggesting that the presence of robust clinical evidence is not a key factor behind its emergence and growth. In this paper, we start from this observation to explore the variety of forms of evidence used in marketing direct-to-consumer SCBIs.

Specifically, we extend an earlier characterization of stem cell clinics in the Southwest United States (Frow et al., 2019) to present a detailed account of the different forms of evidence used on their websites. This study fits into a growing body of research focused on the marketing strategies of stem cell clinics. It complements content and discursive analyses of the marketing strategies around SCBIs, which identify specific types of appeals made in promoting regenerative medicine practices (Rachul et al., 2015; Munsie et al., 2017; Knoepfler et al., 2017; Erikainen et al., 2020a). The forms of evidence we identify overlap substantially with the “tokens of legitimacy” identified by Sipp et al. (2017). We build on the categorization offered by Sipp et al. (2017) and the empirical account provided by Munsie et al. (2017), and here present a small sample of the frequency with which different forms of evidence are used in marketing SCBIs. We highlight which specific “tokens of legitimacy” are more- or less-routinely drawn upon, and in doing so identify priorities for potential action. Our dataset reveals the “ambiguity” of much of the evidence presented by clinics, where the form of evidence itself might have some scientific or medical standing (for example, the peer-reviewed scientific paper) but where the interpretation of this evidence is highly context-dependent. By focusing on ambiguity, we draw attention to the interpretative responsibility faced by prospective patients in navigating the SCBI marketplace, in the United States and beyond.

RESULTS

Businesses offering SCBIs use many forms of evidence in marketing their services. In characterizing 59 stem cell businesses in the Southwest United States, we identified and tabulated the frequency of 13 different forms of evidence (Figure 1), loosely ordered along a spectrum from more scientifically credible to less scientifically credible forms of evidence. Overall, few marked differences were noted between businesses focused exclusively on stem cells (sole-focus businesses), and businesses for which stem cells were a main offering but not the only kind of intervention on offer (main-focus businesses).

As indicated in Figure 1, most businesses marketing SCBIs tended to use forms of evidence that fall in the middle of the evidence spectrum. More specifically, these businesses commonly used scientific language or jargon in marketing their services, but infrequently cited or invoked what might be considered gold-standard forms of scientific
or clinical evidence. For example, there was almost-ubiquitous use of general descriptions of stem cells that presented authoritative, “textbook”-style information (n = 58, 98%) without providing credible references to support this information. Technical descriptions of the medical procedures on offer were present on over 80% of the business websites examined. The level of technical jargon varied among businesses, with most defining key technical terms used and presenting them in accessible ways. A common format for conveying technical information about the theory and practice of regenerative medicine was through the use of a “frequently asked questions” section (n = 37, 63%).

Clinical data
Direct-to-consumer stem cell businesses invoked clinical data in multiple ways on their websites. Registered clinical trials were mentioned by four of the 59 businesses. Three businesses mentioned being actively involved in active clinical trials, and the fourth provided a link to a published clinical trial they had not been involved with. A further five businesses mentioned clinical trials, but these had not been formally registered with clinicaltrials.gov and no results were available on the clinic websites.

A quarter of businesses (24%, n = 14) provided some non-peer-reviewed clinical data on their websites, for example mentioning the number of patients they had treated and/or referring to aggregated patient outcome data. Half of these businesses (n = 7 of 14) were associated with one of the three main direct-to-consumer SCBI franchises in the United States (Regenexx, Cell Surgical Network, and R3).

A more common approach to presenting information about clinical outcomes of SCBIs was in the form of patient testimonials (n = 42 businesses, 71%), either as written quotations or video testimonials from individuals presenting themselves as satisfied patients. These invariably described positive treatment outcomes and/or offered...
glowing reports of the care provider and treatment process. A smaller number of businesses (n = 12, 20%) mentioned celebrity figures (often athletes) who had pursued SCBIs; little clinical information was typically provided in these instances, and outcomes were rarely mentioned.

Peer-reviewed scientific papers
Of the 59 businesses characterized, 21 listed specific, peer-reviewed scientific journal articles on their websites as evidence in support of SCBIs. These 21 businesses cited a total of 261 journal articles published in 170 different journals. Approximately 10% (n = 27) of the articles were published in leading stem cell and scientific journals (as listed by Knoepfler [2020]); fewer than 1% (n = 2) were published in potentially predatory journals (as defined by Beall’s list, see https://beallslist.net/).

In citing research papers, about 25% of businesses (5 of 21) offered a commentary or summary of the article findings; the rest provided a citation but did not offer any interpretation of the research findings for prospective patients. Further analysis revealed an ambiguous relationship between the research papers cited and the specific treatments on offer at the clinic citing the paper (Figure 2A). We evaluated each of the 261 journal articles with respect to the SCBIs marketed by the business citing them. Only 2% (n = 6) of the articles presented direct evidence in support of the specific treatments being offered by the clinics referencing them – that is, they described human clinical studies involving the same kind of (minimally manipulated) stem-cell-based preparation to treat the same medical condition offered by the clinic.

A further 75% of the articles cited (n = 195) did focus on clinical applications of stem cells, but the findings presented did not lend direct support for the specific interventions marketed by the business citing them. We categorized this set of papers as offering “ambiguous” evidence with respect to the services offered by the clinic (Figure 2B). The reasons for including a journal article in this category included (1) reporting on an animal rather than a human study, (2) using cultured stem cells (rather than the
minimally manipulated preparations typically used by the businesses under investigation), (3) using different cell preparation methods compared with the clinic, (4) using a different type of stem cell compared with the clinic, (5) reporting on a medical condition not treated by the clinic, (6) not including a control group in the study, and (7) not reporting that the SCBI was more effective than the control at treating the condition under investigation. Approximately half the papers (n = 126, 48%) met one of these criteria; the other half (n = 135 papers) fell into multiple of the listed criteria.

Medical qualifications of care providers
Stem cell businesses typically listed the medical qualifications of their care providers (85%, n = 50, Figure 1). The biographies of care providers frequently mentioned board certifications and membership of professional associations (Figure 3A). Other markers of credibility included mentioning awards and making it onto magazine lists of “top doctors.”

Approximately 70% of the businesses characterized listed at least one board-certified doctor. About 50% of the care providers listed on the websites of sole-focus clinics were board-certified, and 34% in the main-focus clinics. The medical specialties of the board certifications were varied, with the highest number of care providers certified in specialties relating to sports medicine and rehabilitation, general medicine, and cosmetic practices (Figure 3B).

A total of 34 different medical boards were represented among the care providers across the 59 businesses characterized. Of these 34 boards, 13 are represented by the American Board of Medical Specialties (ABMS), three by the American Osteopathic Association (AOA), and the remaining 18 are independent medical boards (Table S2). Notably, all 25 care providers board-certified in sports medicine and rehabilitation listed certification by the American Board of Physical Medicine and Rehabilitation (a member board of ABMS). In contrast, the 10 care providers listing board certification in alternative medicine were certified by nine different medical boards. Another four care providers listed...
board certifications in regenerative medicine, all certified by the American Board of Anti-Aging and Regenerative Medicine (an independent board established in 1992).

Similar heterogeneity was observed with respect to the professional associations listed by care providers (Tables S3 and S4). Over 80 different professional associations were listed by care providers, with associations connected to general medicine and alternative medicine being most represented. In total, seven care providers listed affiliations with two organizations representing regenerative medicine: the American Academy of Anti-Aging Medicine, and the International Federation for Adipose Therapeutics and Science.

Regulatory status of SCBIs
Just over half of the stem cell businesses mentioned the Food and Drug Administration (FDA) on their websites (n = 33). Mention of the FDA was more prevalent on the websites of sole-focus businesses (n = 19, 70%) than main-focus ones (n = 14, 45%) (Figure 4A). Similar proportions provided disclaimers on their website regarding the regulatory status of SCBIs (n = 19 sole-focus and n = 17 main-focus businesses). These disclaimers avoided using language regarding the safety of SCBIs, and explicitly distanced the clinics from any claims about efficacy or the curative potential of SCBIs.

Mentions of the FDA were not uniformly about clarifying the unregulated status of SCBIs (Figure 4B). For sole-focus businesses, 56% (n = 15) included explicit statements that the interventions they offered had not been FDA-approved. But 15% (n = 4) made statements invoking the FDA that could be construed as misleading if a reader was not fully aware of the unregulated status of SCBIs. For main-focus businesses, 16% (n = 5) made explicit statements about the unregulated status of their interventions, and the proportion making potentially misleading statements increased to almost 30% (n = 9). These statements took multiple forms, as detailed in Table S5. For example, a business might suggest that their interventions do not require FDA clearance, or claim they are using FDA-registered facilities and devices, without explicitly mentioning the regulatory status of SCBIs. In two cases, businesses made explicit claims that their SCBIs had been FDA-approved.

DISCUSSION
Our study of direct-to-consumer stem cell businesses in the Southwest United States offers detailed insight into the forms of evidence mobilized by these clinics in promoting their services. In 2016, Turner and Knoepfler identified that the Southwest states captured approximately one-third of the SCBI marketplace in the United States, and included four of the seven “hot-spot” cities (Beverly Hills, Los Angeles, Phoenix, and Scottsdale). While our study reports on a relatively small and geographically contained sample,
we suggest the forms of evidence we identified are repre-

sented on the websites of direct-to-consumer stem cell clinics across the Southwest and the United States more generally, and that similar patterns in frequency of use are likely. Several of the forms of evidence we identify have also been observed on the websites of stem cell clinics in Australia and Japan (Munsie et al., 2017), but with little documentation regarding their frequency of use.

We identify that stem cell businesses do not rely extensively on gold-standard forms of scientific evidence like randomized clinical trials, nor do they frequently cite patented products or procedures in support of their services. Rather, we observe that they rely extensively on forms of evidence that we describe as scientifically or medically ambiguous. By ambiguous evidence, we mean that there is a scientific or medical basis to the information being mobilized, but the interpretation of this evidence is highly context-dependent. Forms of ambiguous evidence mobilized by DTC clinics include (1) highlighting the training and expertise of the clinic care providers, (2) relying heavily on the use of scientific and technical jargon, (3) citing peer-reviewed scientific research papers, and (4) invoking patient testimonials. We use the term ambiguous to draw attention to the gray areas that are made visible when these forms of evidence are put under scrutiny by researchers and/or prospective consumers. This term also highlights the responsibility placed on individuals to interpret the evidence. We briefly discuss each of these gray areas below.

Training and expertise of care providers
Surveys show that the public views board certification as an important consideration when choosing a physician (Gallup, 2003; Freed et al., 2010). However, board certification alone does not mean a physician is qualified to perform regenerative medicine treatments; the specific nature of their qualifications must be considered. There are currently no ABMS or AOA medical boards focused on cellular or regenerative medicine. Furthermore, the heterogeneity in medical boards (>30 boards) represented by the care providers working at the sampled businesses suggests there is currently little consistency in training and oversight of the regenerative medicine interventions offered by these clinics. While board certification is nominally a marker of clinical expertise, experimental and unregulated interventions pose more of a challenge for prospective patients in determining whether the specific credentials of a care provider are appropriate to the treatment they are seeking.

Textbook-style jargon
Textbooks present authoritative views about the current state of knowledge in science and medicine, without neces-
sarily relying on detailed referencing to support each fact or point. Critical to the authority of a textbook is the credi-
bility of the author(s), with core textbooks in science and medicine typically authored by leading, trusted figures in their respective fields. The technical descriptions of stem cells, regenerative medicine, and treatment options detailed on almost all the DTC clinic websites analyzed in this study are written in “textbook” style, but it is not clear exactly who the authors are and what authority or expertise they bring to the table. As such, evaluating the accuracy of the claims made becomes more challenging.

Scientific research papers
About one-third of the DTC stem cell clinics analyzed here cite one or more scientific research papers in support of the services they offer. These articles are published in peer-reviewed, credible scientific journals, and so at face value can be understood to present sound scientific findings. The key challenge for prospective patients is in interpreting whether the specific details of a cited study lend support for the particular treatment they are seeking. Our analysis identifies that this is very rarely the case, with fewer than 2% of the cited papers reporting clinical improvements in humans using exactly the same kind of same-day, minimally manipulated cell preparations offered by DTC clinics. Prospective patients are left to interpret the relevance of any differences between findings of published studies and the specific treatment they are considering.

Patient testimonials
There is a long history in medicine of publishing case reports that focus on a single individual. Acknowledging that patient testimonials are clearly not equivalent to case reports, we nonetheless identify that there is some tolerance within the medical profession for sample sizes comprising one individual. A number of case reports have been published in recent years highlighting adverse effects faced by small numbers of individuals in response to unregulated SCBIs (Dlouhy et al., 2014; Dobke et al., 2013; Kuriyan et al., 2017). The content of medical case reports is very different from patient testimonials, with the latter being almost exclusively cherry-picked by a business to reflect well upon its practice and its care providers (if indeed the testimonials are provided by real patients of the clinic). These testimonials may be persuasive to potential customers, and may indeed report on genuine clinical improvement experienced by an individual; however, they cannot offer certainty regarding the cause of improvement – an unresolvable ambiguity that a prospective patient must contend with in interpreting such testimonials.
Conclusions
Direct-to-consumer stem cell businesses use many forms of evidence in marketing SCBIs online. The findings from this study highlight the significant interpretive responsibility placed on individuals when it comes to evaluating the credibility of a given business— they would ideally attend to the type of evidence and its specific content, as well as the context in which it is presented. For prospective patients seeking to do their due diligence, our analysis highlights the following questions:

- Are the qualifications of the care providers at the clinic appropriate for the specific treatment being sought? What is the history and credibility of a given medical board in certifying practitioners?
- Do the research studies cited on the clinic’s website provide direct and unambiguous support for the specific treatment being sought?
- Is the clinic explicit about the current regulatory status of experimental SCBIs?

We see roles for professional societies and regulatory agencies in helping to navigate these questions. Medical boards can make explicit statements about their position with respect to SCBIs. In our sample, the American Board of Physical Medicine and Rehabilitation (ABPMR) stands out among the 30+ medical boards listed by clinic practitioners, with 25% of the board-certified practitioners citing certification by the ABPMR. Understanding whether the ABPMR offers explicit training in SCBIs or regenerative medicine, and what its position is with respect to such treatments, could be informative for prospective patients in evaluating the expertise of physicians certified by this board.

Professional societies like the International Society for Stem Cell Research (ISSCR) can offer detailed guidance on factors to consider when reading scientific journal articles about stem cells; our analysis identifies several variables to include in such guidance. This list might also be relevant to the Federal Trade Commission (FTC) for their role in protecting consumers from deceptive marketing practices around SCBIs (FTC, 2018), as it provides criteria against which to evaluate whether published materials offer a clear evidence base for specific SCBIs. We identify that most clinics citing peer-reviewed scientific literature on their websites are not citing studies that report on the specific interventions they offer, calling into question the evidence base of their marketing claims. Furthermore, about half the clinics in our sample do not make explicit statements about the unregulated status of the SCBIs they offer; this might also be a productive area of focus for the FTC.

Finally, while these are steps that can be taken by the scientific and medical establishment to restrict deceptive practices and assist prospective patients with interpreting evidence, we note the limitations of such efforts for scientists, medical practitioners, and regulators concerned about the very existence of the direct-to-consumer SCBI marketplace. Making prospective patients aware of the “unscientific” or less scientifically legitimate nature of particular forms of evidence is unlikely to eliminate demand for SCBIs (Brown, 2009). Our empirical findings showing the multiple forms of evidence presented by stem cell clinics lend support to work describing direct-to-consumer SCBIs as straddling an increasingly blurred line between medicine and “biomedical ‘lifestyle’ products” (Erikainen et al., 2020; Saukko et al., 2010). The socio-political context in which this marketplace has emerged is one in which individuals are increasingly framed as consumers rather than patients, and are expected to take active roles in promoting and advocating for their own health (Erikainen et al., 2020). Many of the businesses characterized here use language that positions the prospective consumer as being in charge of their own health and challenges traditional sources of expert advice. Our study offers a baseline characterization of the frequency and types of evidence used by DTC stem cell clinics. We call for more empirical work to understand the priorities and logics used by prospective consumers when considering experimental SCBIs (Petersen et al., 2013; Rachul, 2011; Waldby et al., 2020), and specifically how they approach and interpret the many forms of scientifically and medically ambiguous evidence that currently exist in the SCBI marketplace.

EXPERIMENTAL PROCEDURES
We gathered publicly available material from the websites of stem cell businesses, focusing on forms of evidence used in marketing their services, as well as any statements regarding the regulatory status of the SCBIs on offer. Data collection was performed between late July and early September 2020. We began with the 169 businesses characterized in Frow et al. (2019), which used Internet search terms including the six Southwestern states (Arizona, California, Colorado, Nevada, New Mexico, Utah) and large cities in the Southwest United States to add 41 businesses to the dataset of 128 Southwest clinics published by Turner and Knoepfler in 2016. We then narrowed down this set of 169 businesses to include only those with a “sole focus” or a “main focus” on offering SCBIs; we excluded businesses for which SCBIs were listed as an offering but were not a visible focus of the clinic’s practice, so that the types of evidence presented on clinic websites could be clearly associated with SCBIs. The total number of businesses characterized for this study was 59 (27 sole focus, 32 main focus). This number is lower than the total number of sole-focus (n = 42) and main-focus businesses (n = 65) identified in Frow et al. (2019) owing to clinic turnover (see Supplemental Experimental Procedures for details).
An overview of the data collected for each business is presented, in de-identified form, in Supplemental Table S1. There is great heterogeneity in the terminology and type of information presented on the websites of stem cell businesses. Several broader categories were determined during the process of qualitative data analysis; the categorizations used for care provider specialties and professional affiliations are provided in Tables S2 and S4. Additional details about data analysis methods are provided in the Supplemental Experimental Procedures.

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.stemcr.2021.10.007.

AUTHOR CONTRIBUTIONS

E.K.F. and D.A.B. conceptualized the project. E.K.F. supervised the project. M.C., A.R., and E.K.F. were study investigators. M.C., A.R., and E.K.F. provided data curation and analysis; M.C., A.R., and E.K.F. wrote the original draft. D.A.B and E.K.F. reviewed and edited the manuscript. M.C., A.R., and E.K.F. visualized the project.

CONFLICTS OF INTEREST

The authors declare no competing interests.

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