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The Changing Landscape of Carrier Screening: Expanding Technology and Options?[1]

Michelle L. McGowan, PhD[2], **Deborah Cho, MA**[3], and **Richard R. Sharp, PhD**[4]

[2]Department of Bioethics, Case Western Reserve University, Cleveland, Ohio; Center for Genetic Research Ethics & Law, Case Western Reserve University.

[3]Harvard Law School, Cambridge, Massachusetts.

[4]Center for Genetic Research Ethics & Law, Case Western Reserve University, Cleveland, Ohio; Department of Bioethics, Cleveland Clinic, Cleveland, Ohio; Genomic Medicine Institute, Lerner College of Medicine, Cleveland Clinic.

I. Introduction to Expanded Carrier Screening

Carrier screening (CS) is a mechanism by which women and their partners can learn about their risks of having a child affected by a recessive genetic disorder.[5] A carrier is a healthy individual who is not affected by genetic disease but nevertheless has one copy of a genetic mutation.[6] Couples in which both individuals have a copy of the same genetic mutation are at increased risk of having a child who inherits the recessive genetic disorder.[7] Theoretically, carrier identification and education regarding the inheritance of genetic mutations can serve as a form of "genotypic prevention" by enabling couples to prevent the generational transmission of specific genetic disorders.[8]

CS typically takes place in the context of reproductive healthcare,[9] where results may be used to inform prospective parents of their options regarding family planning and prenatal diagnosis.[10] CS is typically recommended on the basis of a family history of a genetic condition and for populations that have higher incidences of recessive conditions such as the Ashkenazi Jewish population.[11] Some medical professional societies have recommended shifting away from targeting CS based on family history and ethnicity toward population-based CS for all women who are considering pregnancy or are already pregnant,[12] specifically to screen for carrier status for cystic fibrosis (CF)[9] and spinal muscular atrophy (SMA).[14]

In the last few years, CS panels[15] have expanded to evaluate large numbers of mutations associated with a range of autosomal recessive and X-chromosome-linked inherited conditions including CF, SMA, Tay-Sachs Disease, sickle cell anemia and Fragile X

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syndrome.[16] Several commercial laboratories have developed these expanded CS panels and market them to reproductive healthcare providers.[17]Despite the changing technological and commercial landscape of CS in the United States, little is known about the clinical and societal implications of expanding CS efforts to include and detect much larger numbers of genetic disorders. To this end, we report results of a study of professionals with expertise in genetics regarding their attitudes toward prenatal applications of expanded carrier screening (ECS). A primary aim of this paper is to describe genetics professionals' perceptions of the benefits and challenges of expanding prenatal CS. A secondary aim is to situate these genetics professionals' perspectives within the broader landscape of societal debates about appropriate integration of new risk assessment technologies into prenatal care. The results and following discussion demonstrate how new approaches to CS both resemble and diverge from previous prenatal surveillance technologies in ways that are likely to impact clinical practice and pregnant women's reproductive choices and perceived responsibilities.

II. Current Approaches to Carrier Screening

Medical professionals advocate CS prior to pregnancy because a wider array of reproductive options is available to prospective parents before pregnancy than during it, including deciding whether and how to conceive and considering assisted reproductive technologies such as embryonic genetic testing or donor gametes.[18] Pregnant women and their partners who receive positive CS results are limited to either (1) accepting the possible risk and continuing the pregnancy or (2) undergoing prenatal diagnosis and potentially deciding whether to terminate or continue an affected pregnancy.[19] However, preconception applications of CS are logistically challenging: nearly half of all pregnancies in the United States are unplanned, and non-pregnant patients are typically not interested in seeking population-based preconception carrier testing.[20] As a result, CS is typically offered during pregnancy by prenatal care providers, including obstetricians, nurse midwives, and family practitioners who deliver babies.[21] However, there is evidence that not all obstetricians and gynecologists adhere to professional guidelines for population-based CS.[22] To the extent that genetic counselors are involved in counseling regarding CS, their involvement tends to occur after a woman and her partner receive a positive result.[23]

In addition to variability of CS practices across health care providers and patient populations, research has also shown that education and values impact patient willingness to consider CS in the reproductive context. Empirical research suggests that pregnancy itself is a lens through which women make decisions about whether to accept carrier testing, whereby "underlying belief systems, heightened vulnerability and personal stress management strategies" influence decision-making during pregnancy.[24] For instance, Sparbel and Williams found that pregnant women who were committed and attached to their pregnancies were less likely to accept carrier testing to avoid heightening their anxiety and stress.[25] Hence, some have argued that education and informed consent for CS should be tailored to patient values and expectations, as educational needs for making an informed decision about whether to undergo screening differ depending on patient values.[26] However, existing research assessing educational needs and values has been limited to assessing CS for single gene disorders, and little is known about how the expansion of CS panels might impact clinical practice and patient uptake.

III. The Emergence of Expanded Carrier Screening

Despite evidence that there are multiple challenges associated with the integration of population-based approaches to CS into reproductive healthcare, several commercial laboratories are beginning to advocate ECS. The Universal Genetic Test marketed by Counsyl was the first of these products to become available through select clinics across the United States.[27] Unlike population-based CS for individual genetic disorders (e.g., CF and SMA) which is largely administered during pregnancy and CS panels targeted towards specific ethnic populations (e.g., the Ashkenazi Jewish Genetic Panel), the Universal Genetic Test was marketed as a preconception CS panel that would be universally-applicable to all ethnic populations due to the inclusion of genetic mutations that are common across ethnic groups.[28]

Since 2009, four additional products have become available: Ambry Genetics' AmbrySCREEN,[29] GenPath's InheriGen,[30] Pathway Genomics' Pre-Pregnancy Planning Insight,[31] and 23andMe's Personal Genome Service.[32] The five currently available products screen for 47 to 164 autosomal recessive and X-chromosome-linked conditions that range in severity and age of onset from fatal, childhood onset conditions to adult onset conditions.[33] With declining genotyping costs and a thriving commercial market for genetic testing products, it is reasonable to expect that the number of genetic conditions and mutations evaluated by carrier testing products will continue to increase.[34]

These products are marketed primarily as preconception CS tools to be used by prospective mothers and fathers,[35] though there is some evidence that ECS is available to prenatal patients as well.[36] If used in the prenatal context, ECS of the mother may be followed by diagnostic testing of the fetus.[37]

Current ECS products screen a patient-provided saliva or blood sample for known mutations at loci associated with recessive diseases.[38] The patient or physician can expect results in approximately two to three weeks.[39] Prices range from $99 to $450, which is within the range of the costs traditionally associated with evaluation of carrier status for single disorders such as CF or SMA.[40] Most products are offered only through a physician,[41] although one product is available for purchase direct-to-consumer via the Internet.[42] While one product advertises its availability at "100s of clinics across the US,"[43] information regarding uptake of these products is not available currently. In addition, there are no medical consensus statements or professional-society guidelines regarding the use of ECS products in preconception or prenatal care.

IV. Focus-Group Study

Focus-group methodology was used to examine genetics professionals' perspectives on the expansion of CS. This methodology is ideal for collecting in-depth qualitative data, as focus groups involve small gatherings of knowledgeable individuals who share a common set of interests for a moderated discussion of a chosen topic.[44] Focus-group methodology is particularly useful for producing data through social interaction that allows participants to make comparisons between each others' experiences and opinions.[45] This approach enables participants to react to and build on responses from their colleagues, resulting in novel

opportunities for the production of ideas and the identification of areas of disagreement and agreement.[46] The focus-group sessions reported here comprise a component of a larger study to assess genetics professionals' perspectives on the impact of genomic tests on clinical practice.[47]

To promote professional and specialist diversity in each focus group, a purposive sampling strategy was used to identify experts in medical genetics and genetic counseling at academic medical centers with well-established genetics programs. The research team organized focus groups in Ann Arbor, Michigan; Baltimore, Maryland; Cleveland, Ohio; Denver, Colorado; Philadelphia, Pennsylvania; and Seattle, Washington. Sites were selected based on their geographical location, training programs in medical genetics and genetic counseling, translational research programs, and clinical practice settings (e.g. pediatric vs. adult clinics, public vs. private institutions, etc.). With approval of the institutional review board (IRB) at each study site, collaborators at the Cleveland Clinic, Johns Hopkins University, University of Colorado, University of Michigan, University of Pennsylvania, and University of Washington assisted in identifying participants with appropriate expertise in genetics, including specialists in medical genetics, pediatric genetics, genetic counseling, public-health genetics, primary-care medicine, laboratory medicine, health communication, law, and bioethics. These individuals were approached by the Principal Investigator, R.S., and recruited to participate in focus-group sessions. Participants provided written consent to participate and received $100 for their participation.

Six focus-group sessions exploring ECS were conducted in March 2011. A clinical case report was presented to each focus group to examine participants' opinions about the use of ECS in reproductive healthcare. This case report consisted of a hypothetical patient's medical history, reasons for seeking reproductive counseling, and an anonymous laboratory report presenting ECS results from a commercial laboratory. This laboratory was not involved in any aspect of this study. The ECS product discussed at the focus group sessions must be ordered by a licensed physician and evaluates approximately 350 recessive mutations associated with 78 genetic diseases. R.S. served as a facilitator for the focus groups and used a moderator guide to promote consistency across sites.

Discussions of ECS lasted approximately 30–60 minutes. Participants were asked to consider how they would prepare for a clinical appointment in which they reported test results to this hypothetical patient and counseled her about reproductive implications. Additional questions examined participants' attitudes about the clinical implementation of ECS, including participants' opinions about whether ECS might be preferable to more targeted approaches to CS based on a patient's family history or ethnicity. Participants were asked to identify potential challenges in the interpretation and communication of ECS results and to describe their overall levels of enthusiasm for ECS.

Focus-group discussions were audio-taped and transcribed to enable thematic analysis by independent review and consensus-building conferences.[48] To promote and construct validity and reliability of conceptual domains identified through coding, M.M. and D.C. analyzed focus-group transcripts to capture themes and concepts related to applications of ECS using qualitative data analysis software (ATLAS.ti v5.8). Using methods prescribed by

grounded theory,[49] analysts developed their interpretations of the themes though review of the coded transcripts. The hypothetical case study presented to focus group participants dealt with a preconception CS scenario, and findings related to preconception applications of ECS will be presented elsewhere. Thematic analysis presented here is limited to examining participants' opinions of prenatal applications of ECS.

V. Results

Forty genetic professionals participated in six focus groups for this study. Four themes related to prenatal applications of ECS emerged from the focus-group discussion transcripts.[50] *First*, participants suggested that the appeal of ECS in the prenatal context may be that it tests for more risk factors at a comparable or lower cost than standard CS. *Second*, participants felt that the marketing of ECS as a preconception CS tool was not likely to have an impact on the timing in which CS tends to be introduced into patient care. *Third*, participants felt that uptake of ECS may foster a defensive approach to prenatal care for both clinicians and pregnant women. *Fourth*, participants stressed that informed-consent practices for prenatal screening tend to be inadequate and that the challenges associated with effective prenatal risk counseling may be exacerbated in the context of ECS. We present these major findings in greater detail below.

Participants suggested that the appeal of ECS in the prenatal context may be that it assesses more risk factors at a comparable or lower cost than other targeted and population-based CS tools. As one participant explained:

> I've talked with some of the prenatal counselors about these tests and I think there is still a debate about exactly how to handle them because it is such large testing and for people who aren't seeing these conditions all of the time it gets harder to counsel about it. But I think a lot of people are feeling more like if you're going to offer CF screening, you might as well … just offer the whole thing.[51]

Although ECS was attractive to some participants based on its cost and scope of coverage, others noted that even women who might want to avoid invasive prenatal diagnosis are still likely to be offered some forms of genetic screening during pregnancy, especially if preconception CS results or maternal age indicates increased risk for the child.[52]

Notably, participants cited the commonality of prenatal (as opposed to preconception) screening for carrier status for CF and Tay-Sachs disease. Participants rejected the idea that the commercial availability of ECS panels would have an impact on *when* CS is introduced to patients.[53] Rather, participants remarked that preconception genetic counseling is atypical, and that patients are much more likely to be introduced to CS for the first time when they are already pregnant.[54] Though these products are primarily marketed as preconception risk assessment tools, one participant explained, "[i]t is worth noting that these tests are used prenatally, they're not used pre-conception …. The language is around preconception because that's what … the companies want to sell, but the testing is actually done after a woman's pregnant."[55]

In contrast to screening for aneuploidies[56] and other prenatal risk factors that are not related to genetic contributions from the parents, participants characterized CS as "one of the areas where it is easier to walk parents through the choices that they have."[57] However, they acknowledged that these choices are constrained and potentially difficult for pregnant women and their partners because reproductive options that are available to those receiving positive CS results in the context of an ongoing pregnancy are all *reactive* as opposed to *proactive*.[58] Participants explained that the pathways that were available to pregnant women and their partners include prenatal diagnosis followed by possible termination of the pregnancy if a fetus is affected by mutation in question or continuation of the pregnancy without additional testing of the fetus and accepting the risk of having an affected child.[59]

While these reproductive options may be confounding for prospective parents, participants noted that increasing use of ECS by clinicians and pregnant women may signal a more defensive approach to risk identification and management.[60] As one participant elaborated:

> This is going to be really driven on the defensive medicine side, right? So we know for a fact that there are wrongful birth causes of action that go through because you've failed to pick up something that you needed to pick up in a test. So this will drive both sides—certainly the medical side to use the most comprehensive test possible—but there's also enormous pressure, I think, on women in particular to, you know, take whatever step you can take to have a healthy baby, as crazy as that stuff is going to be…. When you look at some of the psychological literature about why women agree to testing during pregnancy even some of whom will say, "But I would never, I would never abort the fetus," but who will still agree to do the testing. It's sort of an interesting—and they're not saying it just because I want to know the information, they feel very pressured to do things.[61]

This quote suggests that among future users of ECS products, many may be clinicians hoping to avoid wrongful birth lawsuits and pregnant patients who want to avoid having children with detectable genetic diseases. Participants noted that this defensive stance could be challenging in two ways: while ECS may assess risks that standard approaches to population-based CS would miss, it does not assess every possible reproductive risk factor. Some participants cautioned, for instance, that ECS products do not evaluate a woman's risk of having a child with chromosomal anomalies such as aneuploidies (which increases as a woman ages), so ECS should not be considered adequate for assessing all genetic and chromosomal risks.[62] Participants cautioned that a defensive approach to CS could be confusing for both clinicians and patients given that ECS is both more inclusive, but not comprehensive in its assessment of genetic and chromosomal risks.[63]

Illustrating the complexities of integrating new and more complex risk assessment tools into prenatal screening and testing, one participant drew parallels between ECS and cell-free fetal DNA testing,[64] saying that both of these emerging tools are "not quite ready for prime time."[65] Despite their professional assessments that new prenatal screening tools were outpacing clinicians' capabilities to develop plans for responsive integration of these genetic technologies into healthcare, participants argued that reproductive specialists can impact the integration of ECS in important ways, such as by developing appropriate strategies for obtaining informed consent and providing effective pre-test counseling.[66]

Participants agreed that uptake of ECS by pregnant women should be voluntary, but they acknowledged that prenatal testing is sometimes undertaken without adequate informed consent.[67] Giving the example that many pregnant women do not know that they have undergone routine prenatal genetic screening if it only involves a blood draw,[68] one participant noted:

> I think that these [ECS panels] are going to be marketed to OBs, and they're just going to do them without a conversation. The same as they kind of do triple screens and quad screens without much of a conversation for pregnant women; and then we're [genetic professionals are] going to be left hoping that we can help with the interpretation.[69]

Participants in another focus group also stressed that obtaining informed consent would be especially challenging in the context of ECS because of the wider range of disease risks assessed.[70] The previous quote also illustrates that specialists in genetics saw themselves as being put in the position to interpret ECS results that were ordered by other clinicians, perhaps with inadequate pre-test counseling. In this context, genetic professionals were especially concerned that pregnant women and couples may not appreciate that pursuing ECS may later require them to consider prenatal diagnosis and possibly pregnancy termination based on genetic findings.[71] The general consensus among participants was that the limitations of current ECS products should be discussed with pregnant women and couples prior to testing and that "a responsible approach to practice would emphasize pre-test counseling … because you want to make sure that she understands what the limits of her options are before she gets the test."[72]

VI. Prenatal Applications of ECS: Expanding Technology and Options?

Advocates of ECS suggest that it is preferable to conventional CS due to its disease coverage and applicability across ethnic populations.[73] As ECS products become increasingly available, a wider range of women and their partners may discover that they carry a recessive mutation that may be inherited by their children. The findings of this focus-group study suggest that the introduction of ECS into prenatal care presents challenges that both resemble and diverge from conventional approaches to prenatal CS. These challenges relate to timing of implementation, informed consent, counseling, and maternal attitudes and perceived responsibilities. Each challenge will be discussed in turn.

In some ways, the promises and challenges of ECS that study participants identified reflect long-recognized issues regarding the integration of genetic risk information into reproductive healthcare and are not unique to ECS technology. Historically, the evaluation of new prenatal screening technologies has advanced with the dual goal of increasing the amount and specificity of risk information along with reduction of costs.[74] Hence, participants' suggestion that prenatal care providers may be drawn to ECS because it provides more risk information at a lower or comparable cost to other CS platforms may reflect the likely continuation of this trend.[75] As mentioned in the focus groups, the appeal of ECS may also reflect conservatism on the part of clinicians trying to avoid liability for not detecting genetic conditions prenatally.[76] However, existing problems of implementing

and counseling for prenatal CS may be compounded by the timing of screening, volume of results, and rarity of diseases included on panels.

Edelson has argued that the success of population-based CS programs may be dependent on "tight coupling between diagnosis and clinical outcome, the clear implications for specific action which the identified 'carrier status' has, and the relatively brief and well-defined time span within which persons have to act with regard to the information."[77] The findings of this study and previous research suggest that it is likely that most women will receive CS results during pregnancy, which makes for a well-defined, yet compressed decision-making timeline.[78] Hence, women who receive abnormal CS results in the context of pregnancy will need to consider whether to use prenatal diagnosis and whether to terminate or continue an affected pregnancy.[79] The timing of the testing will impact the utility of the information provided, regardless of whether the technology is screening for a single gene mutation or for a number of recessive mutations. Thus, it is important that both clinicians and pregnant women view this technology in light of how timing of implementation can affect the choices that would follow.

Further, the findings of this study suggest that challenges associated with informed consent for ECS will be significant. Many of these challenges are already anticipated in experiences with other non-invasive prenatal screening technologies such as CS for single gene disorders.[80] Some explanations for inadequate informed-consent processes for screening in the prenatal context include the brevity or absence of pre-test counseling and the common (thus potentially unremarkable) occurrence of blood draws during prenatal appointments.[81] These challenges may reflect constraints on the ways in which prenatal appointments and practices are organized more than the risk assessment technologies in question.

In addition to the parallels drawn between ECS and existing prenatal screening technologies, study participants also identified new challenges potentially posed by the integration of ECS into prenatal care. Research has demonstrated that women with known heritable genetic risk factors tend to be ambivalent about the range of reproductive options available to them, and their attitudes fluctuate as they encounter new stages in their reproductive journeys.[82] As with the normalization of past reproductive genetic screening and diagnostic technologies,[83] participants suggested that ECS may exacerbate an already complicated prenatal decision-making process by introducing more and rarer carrier traits to be evaluated, increasing the complexity of pre-test counseling and interpretation of results, and increasing the volume and uncertainty associated with positive results.[84] As has been argued regarding the inclusion of three or more conditions in prenatal screening panels, "it is likely that efforts to educate screenees about an increasing number of diseases will not be as successful, as there will probably be a limit to the number of disease descriptions that even a highly educated screenee can recall after a single education session."[85] This challenge may only be amplified in the context of ECS panels, which screen for upwards of 45 conditions at once.[86] In addition, the range of diseases examined by ECS products further complicates the process of obtaining informed consent and may require substantially more time to review in comparison to more familiar prenatal evaluations. Thus, moving from population-based screening of single gene disorders to ECS panels which include screening for a large number of rare disease-associated mutations may limit the effectiveness of counseling for pregnant

women regarding reproductive decisions and amplify uncertainty about how to manage results concerning rare disorders.

The inclusion of more disease risks in CS panels brings with it the increased possibility that more pregnant women will receive positive results, potentially making identification as a carrier "the new normal." This new normal is likely to have implications for many more pregnancies, which in turn could impact women's attitudes toward their pregnancies. One challenge that participants noted is that if some women are already under-informed about the kind of prenatal screening done, then unexpected positive results could be that much more challenging to assimilate into one's frame of reference.[87] This may reflect an understanding by genetics specialists, as Lyerly and colleagues have argued, that the drive to infuse more risk information into pregnancy is not always balanced against the values of pregnant women and their families.[88] Findings of this study suggest that under-informed patients receiving positive ECS results may be faced with unexpected and difficult decisions without adequate preparation. Some of these choices may concern the continuation of a pregnancy and other potential costs of managing the risk. For instance, although ECS products are currently priced to be affordable at $99 to $450, follow-up procedures will be much more costly. The cost for follow-up in the form of genetic sequencing and prenatal testing may present significant barriers to making test results actionable.[89] Being under-informed about the analytic limitations of the screen may also result in patients who accept ECS, receive negative results, and later have a baby with a genetic or chromosomal disorder that they believed to be ruled out by the screen.

On the other hand, participants suggested that some pregnant women will be drawn to ECS in their quest to ensure the birth of a healthy baby. The expansion of CS may exacerbate what has been characterized as the onus on women to take "genetic accountability" for their pregnancies by seeking genetic risk information.[90] For these women, as has been documented with users of amniocentesis and prenatal CS for single gene disorders,[91] there may be a sense of maternal obligation to learn what they can about the health of their prospective children and to make decisions regarding downstream implications of screening. This represents what Reed has characterized as a perceived responsibility by pregnant women to manage genetic risks to the fetus even when genetic material that confers risk is equally contributed by both men and women as carriers.[92] However, as this study and others have shown, there is no prenatal screen or diagnostic tool that can rule out all possible reproductive risk factors.[93] Participants raised the concern that the drive to ensure health on the part of pregnant women may create unrealistic expectations—both concerning the technology in question and of the profession of medicine. These shifting expectations could, in some cases, have legal implications. For example, there is a potential for wrongful birth lawsuits to increase.[94] Patients with babies with genetic disorders covered by ECS panels but who were not offered ECS may feel they were denied access to the most comprehensive risk information available.[95] There is also the possibility that false negative and false positive results of ECS could prompt wrongful birth lawsuits.[96]

While the desire for the "perfectly normal" baby has been well-documented in the social science literature,[97] the marketing of ECS as a "universal" or "comprehensive" carrier test may contribute to conservatism on the part of clinicians trying to avoid liability and increase

patient tentativeness toward pregnancy in problematic and unrealistic ways. Juengst and colleagues have argued that "the logic of prevention has already walked some expanded carrier-screening companies across the equivocal bridge between phenotypic and genotypic prevention, though these are still firmly in the realm of individual rather than public health interventions."[98] Although study participants framed ECS in terms of the individual doctor-patient interaction, the question remains as to whether and how increasing identification of carriers through the expansion of population-based CS may contribute to shifting responsibility for genotypic prevention from the choices of individual women to social mandates to act in ways that would ensure fetal health as has been seen with the criminalization of pregnant drug users.[99]

VII. Conclusion

This study provides a vantage point from which to assess the potential impact of expanding the scope of population-based carrier testing in the prenatal setting. What we learned from focus groups with genetics professionals about expanding CS in the prenatal context suggests that clinicians and pregnant women will likely face similar logistical and psychosocial challenges as those that have arisen in the context of population-based CS for single gene disorders and other forms of prenatal screening. Although ECS promises to provide more information regarding one's genetic risk factors, clinicians and their patients may encounter additional vulnerabilities in light of information provided by ECS, particularly if these tests provide unexpected results. Further research is indicated to anticipate the individual, professional, legal and societal implications of expanded carrier screening.

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14. Spinal muscular atrophy is a childhood or adult-onset life-limiting neuromuscular disorder that is inherited in an autosomal recessive manner. Prior, *supra* note 6, at 840.
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50. The IRB-approved research protocol requires that focus group transcripts remain confidential and on file with study personnel. Please direct any queries about the focus group data to Dr. Richard Sharp (sharpr3@ccf.org).
51. Focus Group 2.
52. Focus Groups 2–6.
53. Focus Groups 2 & 6.
54. Focus Groups 5 &6.
55. Focus Group 6.
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58. Focus Groups 3 & 6.
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