

Impact of Expanded Carrier Screening on Health Care Utilization

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As the cost of genomic sequencing has declined in recent years, many health care providers and payers have begun offering expanded carrier screening (ECS) to women and their partners planning a pregnancy. Carrier screening is genetic testing for a patient who does not have a personal or family history of a genetic disorder to determine whether they have any gene variants associated with a disorder. Screening prior to pregnancy allows couples to consider the full range of reproductive decisions, including preimplantation genetic diagnosis, use of donor sperm or egg, or not to have children, should they be found to be at risk of having a child with a genetic disorder. Currently, the American College of Obstetricians and Gynecologists¹ recommends carrier screening for cystic fibrosis (CF) and spinal muscular atrophy (SMA) for all women planning a pregnancy, and obstetrical and gynecological providers are familiar with these screening tests. CF is the most common life-threatening, autosomal recessive condition in the non-Hispanic White population, and SMA is a leading genetic cause of infant death.¹ Typically, women are tested first, and male partners are tested only if a woman is found to be a carrier of a condition. Unlike the single-gene carrier screenings used to test for CF and SMA, most ECS tests cover a few dozen to a few hundred recessive or X-linked conditions, many of which most providers have no experience with, in couples with no known risk factors for these conditions.^{2,3} Almost all couples who use ECS will not have increased reproductive risk because these genetic conditions are rare, with an expected prevalence of 1% to 2% in an unselected population.⁴ Although ECS could have substantial direct and indirect effects on couples' reproductive decision-making in the face of a positive result,^{5,6} much less is known about how the more common negative (normal) results affect decision-making and resource use within a health system. Better understanding of downstream health care utilization in patients with negative results, defined as a reproductive risk of less than 25%, is needed as payers and providers consider the implementation or expansion of carrier testing and screening programs. If ECS causes increases in unnecessary utilization because of patient stress generated by the ECS process, this could indicate negative impacts on patients and could also increase costs for payers.^{5,7-10}

ABSTRACT

OBJECTIVES: To evaluate potential consequences of expanded carrier screening (ECS) for reproductive risk on health care utilization among women who are not at increased reproductive risk.

STUDY DESIGN: Women planning pregnancy were randomized to usual care carrier screening or ECS to assess reproductive risks. Electronic health record (EHR) data were used to evaluate the effects of ECS on pregnancy-related utilization and general health care utilization among all study participants who did not receive positive ECS results of at least a 25% risk (ie, received negative [normal] ECS results).

METHODS: EHR data were extracted through research-ready databases and extensive chart review for 304 participants. We analyzed the effect of ECS for women who were not found to be at increased reproductive risk on (1) utilization of mental health services in the period between randomization and initial results disclosure; (2) utilization of general outpatient and inpatient services, specialty services, and mental health–related services in the year following randomization; and (3) utilization and refusal of pregnancy-related services among pregnant women (n = 129) prior to and following randomization.

RESULTS: No significant differences in health care utilization were found between women randomized to receive ECS and those receiving usual care. Women who received negative ECS results did not refuse recommended screening for conditions that are not identified via ECS at a higher rate than women in the usual care arm.

CONCLUSIONS: These results suggest that ECS does not have unintended negative impacts on the health care system for the majority of patients who are not at increased reproductive risk.

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There are 4 categories of potential harm related to negative ECS results that could affect health care utilization. The first category is that women who receive negative ECS results may refuse recommended screening for conditions that cannot be identified via ECS because they are falsely reassured by their negative ECS results.¹¹⁻¹⁴ For example, an expectant mother may erroneously choose not to receive aneuploidy screening to detect chromosomal abnormalities during pregnancy because of negative results from her ECS. This refusal would lead to lower pregnancy-related health care utilization among women who have negative test results than among women who receive only standard CF screening. The second category of potential harm is that receiving ECS could lead to anxiety or stress while waiting for or receiving test results (due to worry about a positive result) or from misunderstandings about how to interpret results. This could lead to increased use of mental health services, particularly during the waiting period between sample collection and results disclosure.^{11,12,15} The third type of potential harm is an increase in general health care utilization, including primary care and pregnancy-related services, if women request additional care due to misunderstanding their negative genetic screening results. The final type of harm is that individuals may misunderstand what it means to be a genetic disease carrier and think they are affected themselves, when in fact they have a recessive gene for a condition and are not at risk. Previous studies have shown that individuals who are carriers sometimes believe they are affected by the disorder.^{13,16} This could result in additional unnecessary general health care utilization. All these potential harms could be exacerbated if ECS becomes standard of care, especially if the role of ordering the tests and providing results is managed by providers other than genetic counselors or medical geneticists (eg, obstetricians, primary care providers). Health care professionals have reported concerns about adequate provider knowledge, time needed to offer informed consent/genetic counseling, and costs associated with ECS.¹⁴

To address the important concerns about the impact of ECS on subsequent health care utilization, the present preliminary study examined the effects of disclosing negative results from ECS on utilization compared with usual care. We used data from the NextGen study, a randomized controlled trial comparing ECS for 728 inherited conditions with usual clinical care (typically only CF screening was standard care during the study) among women planning a pregnancy.¹⁷ We assessed differences between women randomized to ECS and usual care in terms of (1) utilization of mental health services (outpatient, inpatient, and medication use) in the period between randomization and results disclosure; (2) utilization of outpatient primary care, outpatient specialty care, and inpatient and outpatient mental health services in the year following randomization; and (3) utilization of pregnancy-related services in the 5 years prior to and at any point following randomization among women

TAKEAWAY POINTS

Understanding the consequences of negative (normal) expanded carrier screening results is critical to evaluating the benefits and harms of implementing a systemwide program.

- ▶ There was no increase in mental health service use, outpatient and specialty care use, or pregnancy-related services use following testing.
- ▶ Most literature on carrier screening focuses on patients with positive results. This work expands knowledge on the impacts of the more common negative results.
- ▶ Expanded carrier screening programs are unlikely to have negative effects on mental health, increased health care utilization, or increased patient misunderstandings for individuals with negative results.

with a documented pregnancy. Findings from this study provide valuable information for health system decision makers determining coverage when considering adoption of ECS, given that the most common testing outcome of ECS is a negative result.

METHODS

Study Setting

All women included in this analysis were members of Kaiser Permanente Northwest (KPNW), a large integrated health care system located in the Portland, Oregon, metropolitan area, who had participated in the NextGen study.¹⁸ The NextGen study identified women through the electronic health record (EHR) who had received clinical carrier screening as part of usual care (usually for CF) either before conception or during a prior pregnancy and were at least 6 months post partum. Women were called to assess their intentions for a future pregnancy and were invited to join the NextGen study if they reported plans of any future pregnancies.

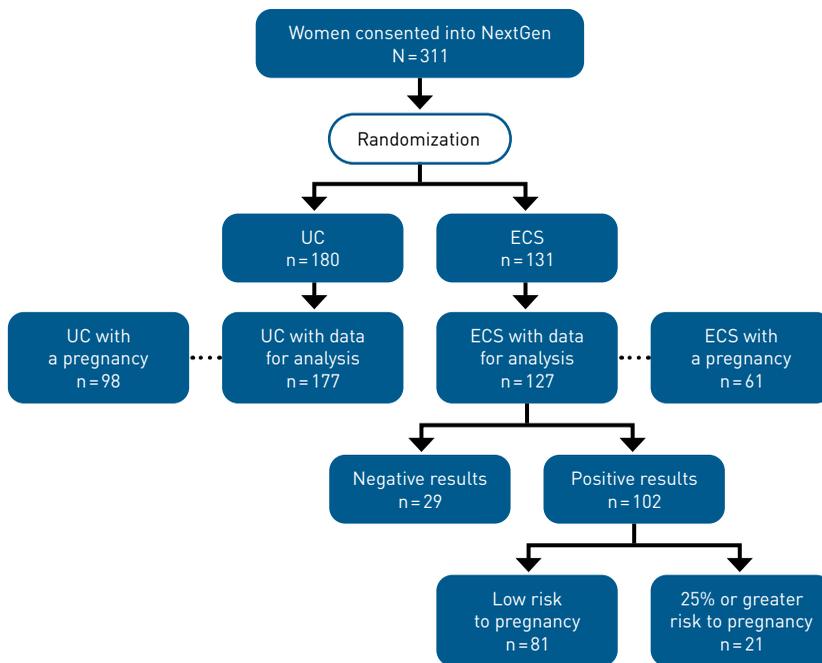
Study Procedures

In an initial visit with a genetic counselor, patients were consented, completed a baseline survey, and were randomized in a 3:5 ratio to either (1) ECS (n = 131), where participants had the option to receive results for an ECS panel of up to 728 autosomal recessive, X-linked, and mitochondrial conditions and 121 medically actionable secondary findings (findings not related to the indication for testing), or (2) usual care (UC; n = 180), where participants received no additional testing beyond the clinical carrier screening that was an inclusion criterion for the study (Figure). All results were disclosed by a genetic counselor at an in-person visit. If women randomized to ECS were found to be a carrier of an autosomal recessive disorder (78% of women), their male partners were invited to receive ECS; 71 men enrolled in the study. Utilization data from male participants were not included in the present analyses because there was no UC group. We evaluated all inferential tests at a 2-tailed α level of .05 and report associated 95% CIs.

Analysis Population

A total of 127 ECS women and 177 UC women had data available for analysis. Seven women were excluded: 2 due to not being KPNW

FIGURE. Study Flow



ECS, expanded carrier screening; UC, usual care.

members (both UC), 1 due to refusing the study immediately after randomization (UC), and 4 in the ECS group who were unable to be reached for results disclosure. For analyses that included the period after results disclosure, we excluded 21 women from the ECS group who had at least 25% risk of having an affected offspring for at least 1 condition. This included women carrying an X-linked condition, women carrying the same autosomal recessive condition as their male partner, and women with an autosomal dominant medically actionable secondary finding or a male partner with such a finding.

Mental Health Service Use Before Results Disclosure

All data for the impact of ECS on service use were extracted through electronic queries of databases populated from standardized fields in the EHR. To determine if there was increased mental health utilization following randomization and ECS testing, but prior to result disclosure, we extracted mental health–related utilization data from the EHR during this time period. We matched each UC participant to the ECS participant who was randomized immediately preceding them and assessed mental health–related utilization over the same follow-up period as the matched ECS participant. Multiple UC participants could be matched to the same ECS participant. ECS participants received their screening results a mean of 117 days after randomization; the time period between randomization and results disclosure varied considerably due to lab turnaround time and scheduling of disclosure appointments.

The mean follow-up period for UC participants was 98 days.

Primary Care and Mental Health Utilization in the Year Following Randomization

We also tested whether ECS affected the amount of outpatient primary care, outpatient specialty care, inpatient mental health care, and mental health medication dispensing in the 12 months following randomization. For all outpatient health care use, we counted the number of in-person visits, telephone encounters, and email exchanges between the patient and provider. For inpatient mental health services and mental health medication use, we created binary indicators of whether a patient was hospitalized for mental health reasons or dispensed 1 or more mental health medications.

Analysis for Mental Health Service Use Before Results Disclosure and Primary Care and Mental Health Utilization in the Year Following Randomization

Outcomes were modeled using a family of count data models and negative binomial regressions to best approximate the discrete, nonnegative nature of health care encounters and account for potential overdispersion.^{19,20} We used months between randomization and result disclosure as an exposure term to account for varying observation times. We considered zero-inflated models for outcomes in which a majority of the participants had zero utilization (mental health and obstetrics/gynecology visits), but they did not considerably improve model fit over the standard negative binomial model.^{20,21} Dichotomous utilization outcomes were modeled using logistic regression. For all models, a significant incidence rate ratio (IRR; count models) or odds ratio (OR; logistic models) greater than 1 for the dummy indicator representing arm (0, UC; 1, ECS) would indicate that those randomized to ECS had more utilization; a ratio less than 1 would indicate less utilization.

Pregnancy-Related Service Utilization

Data for pregnancy-specific service utilization, including ultrasounds and aneuploidy screening, were identified through EHR query. Data were limited to women with a pregnancy lasting 6 months or longer to allow long enough pregnancy duration for the services to be offered. We reviewed data in the 5 years before study entry or at any time after enrolling in the study. Twenty-six percent of pregnancies in our population were excluded because they were less than 6 months in duration.

We accounted for some women contributing multiple pregnancies to the analysis by using mixed-effects logistic regression with

restricted maximum likelihood with person modeled as a random effect. Pre- or post entry into the study (0, pre; 1, post), arm, and the product of study entry and arm were included as independent fixed effect variables. The coefficient of primary interest was the product term, which represents the test of interaction of study entry and arm on the outcome. A significant OR greater than 1 for the product term would demonstrate that the difference in utilization between arms was greater at post entry compared with pre-entry, indicating a moderating effect of randomization on utilization.

Chart Review

Manual chart review was conducted for all participants to assess assisted fertility (intrauterine insemination, in vitro fertilization, donor gametes, preimplantation genetic diagnosis), outside referrals for fertility services, pregnancy dates, genetic testing, and refusal of clinician-recommended screening and diagnostic services.

RESULTS

Basic Demographics

The participants' mean age was 32 years, and most were White, were married, and had a college degree or higher. Age and race/ethnicity were similar between ECS and UC participants (Table 1).

Health Service Use Before Results Disclosure

During the time between randomization and results disclosure (ECS arm) or a matched time window (UC arm), there were no significant differences between the 2 groups in mental health medication dispensing (IRR, 1.03; 95% CI, 0.50-2.12) (Table 2). We were unable to model the occurrence of inpatient mental health encounters during this time window because of the rarity of the outcome.

Impact on Service Use Between Randomization and 12-Month Follow-up

There were no significant differences between ECS and UC in number of outpatient primary care provider encounters (IRR, 0.90; 95% CI, 0.66-1.23), telephone encounters (IRR, 0.80; 95% CI, 0.62-1.05), or email exchanges (IRR, 0.75; 95% CI, 0.55-1.01) between randomization and 12-month follow-up for women with continuous health plan coverage during this window with negative results (ECS: n = 95; UC: n = 162). Additionally, there were no significant differences between arms in inpatient mental health visits (IRR, 1.03; 95% CI, 0.29-3.61) or mental health medication dispensing (IRR, 1.01; 95% CI, 0.55-1.85) during this period (Table 3).

Through a telephone interview conducted as a separate part of the NextGen study, 1 participant did disclose possible unnecessary care in the ECS arm. The participant, a carrier of hereditary hemochromatosis, reported calling her doctor for a blood draw to reduce her iron level, despite being told by the study genetic counselor that she did not have the condition. Chart review revealed that the physician understood that the participant was only a carrier and clarified risk with the participant.

TABLE 1. Demographics by Randomization Status

	Expanded carrier screening (n = 127)	Usual care (n = 177)
Age in years, mean (SD)	32.4 (4.4)	31.9 (4.2)
Non-Hispanic White	75%	78%
College degree or higher	75%	77%
Married	82%	80%

Impact on Pregnancy-Related Services

There were no significant interactions between time of study entry and study arm in first or second trimester screening uptake (OR, 0.52; 95% CI, 0.011-25.0), documented refusals to receive screening or diagnostic tests (OR, 1.80; 95% CI, 0.027-118), or other genetic testing during pregnancy following study entry (OR, 0.24; 95% CI, <0.001-115) (Table 4). We found EHR documentation of 1 woman refusing first trimester screening because her ECS results did not find anything that put her fetus at risk, indicating misunderstanding of the difference between first trimester screening and ECS.

In the 5 years prior to study entry, 97 (35%) women who would later receive negative ECS results had documentation in the EHR of at least 1 pregnancy lasting longer than 6 months. Following randomization, 27 (25%) ECS participants and 43 (24%) UC participants had at least 1 pregnancy. Similar results were observed in sensitivity analyses that used date of results disclosure to define the poststudy interval (data not shown).

DISCUSSION

Results from this randomized controlled trial did not find evidence of harms of ECS on health care utilization in women who were not found to be at increased reproductive risk. Specifically, we found no significant differences in outpatient mental health service use between the study arms in the period between randomization and results disclosure or in the year following randomization; no significant differences in use of primary care and specialty care services in the year following randomization; and no significant differences in utilization of pregnancy-related services following ECS testing.

Overall, these results provide reassurance that ECS did not result in unnecessary health care utilization, nor did it result in avoidance of recommended care because of false reassurance. Of the 304 participants whose data we analyzed, chart reviews identified 2 cases in which ECS screening appeared to lead to inappropriate health care utilization: 1 patient who misunderstood her carrier result and sought treatment for hemochromatosis and 1 patient who attempted to refuse first trimester prenatal screening because she did not understand how this differed from ECS. In the first case, the provider identified the patient's misunderstanding and ensured that she received appropriate care. In the second case, we did not find documentation that the patient was informed of the differences between ECS and prenatal screening. Both cases highlight

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TABLE 2. Mental Health Utilization by Arm During Follow-up Period Between Randomization and Results Disclosure

	Expanded carrier screening (n = 127)		Usual care (n = 177)		IRR or OR	95% CI	P
	Mean (SD) or %	Median	Mean (SD) or %	Median			
Outpatient care encounters	0.33 (1.21)	0	0.31 (1.20)	0	0.94	0.34-2.66	.91
Inpatient care	2%		0%		-	-	-
Mental health medication dispensing	11%		11%		1.03	0.50-2.12	.94

IRR, incidence rate ratio; OR, odds ratio.

TABLE 3. Utilization by Arm During 12-Month Follow-up Period After Randomization in Women With Negative Results Who Have 12 Months of Continuous Membership

	Expanded carrier screening (n = 95)		Usual care (n = 162)		IRR or OR	95% CI	P
	Mean (SD) or %	Median	Mean (SD) or %	Median			
Outpatient primary care encounters	1.55 (1.77)	1	1.51 (1.88)	1	0.90	0.66-1.23	.50
Outpatient specialty care encounters							
Mental health	1.09 (2.99)	0	1.22 (3.47)	0	0.79	0.32-1.93	.60
OB/GYN	4.53 (6.41)	1	4.33 (5.97)	2	0.93	0.63-1.39	.74
Telephone encounters (primary and specialty)	7.12 (5.98)	6	7.75 (8.70)	5	0.80	0.62-1.05	.10
Email encounters (primary and specialty)	7.21 (7.75)	5	8.23 (9.33)	6	0.75	0.55-1.01	.06
Mental health							
Inpatient care	4%		4%		1.03	0.29-3.61	.97
Mental health medication dispensing	22%		22%		1.01	0.55-1.85	.98

IRR, incidence rate ratio; OB/GYN, obstetrics/gynecology; OR, odds ratio.

the importance of provider/patient communication when patients request or refuse services that do not align with clinical indications, particularly when genetic test results may be a source of confusion. There is always risk of patients misunderstanding a test result; we tried to mitigate this risk by having “ideal” conditions in which consent and result disclosure were conducted in person by a genetic counselor. In more “real world” situations, many parts of the process could be very different, including having a provider other than a genetic counselor or medical geneticist ordering ECS, having a less detailed consent process, and having parts of the process taking place via email or phone. In these cases, it will be critical for providers to successfully elicit patient engagement in the discussion of results and assess patient understanding of results by using language

such as “Can you explain why you are saying you don’t want prenatal testing?” to ascertain more information about misunderstanding of results vs valid reasons for testing refusal.

Understanding the consequences of disclosing negative results of ECS is critical to evaluating the benefits and harms of implementing a systemwide ECS program. Because most couples will receive negative results, even a small harmful consequence of testing for these couples would be magnified in a large patient population. The results of this study should reassure decision makers considering uptake or expansion of carrier screening programs that these programs are unlikely to have negative effects on mental health, increased health care utilization, or misunderstandings of results.

Limitations

By conducting extensive chart review of each participant in KPNW’s integrated EHR, we arrived at highly reliable estimates of health care utilization. However, although service refusals for standard-of-care screening should be documented, some refusals of services may not have been documented. Given the randomized nature of our design, underdocumentation of refusals would affect our conclusions only if physician reporting of these data were different between the ECS and UC groups.

Given the relatively small sample in this study, the lack of racial/ethnic and socioeconomic diversity (see Table 1), and the exclusion of male partners in analyses, these results should be considered preliminary. Women could interpret negative results differently depending on their background or available resources. Future studies in a more diverse population are needed. Additionally, all women received

pretest genetic counseling and all women with positive carrier results received in-person posttest genetic counseling, both of which served to minimize the risk of misunderstanding of results. It may not be feasible to provide genetic counseling to all women if ECS is offered as standard practice. Obstetricians, who already deliver negative results for a limited number of genes, could disclose carrier results for a larger panel, but additional training may be required to ensure that obstetricians have sufficient knowledge of these conditions to help patients interpret their results. Negative results could also potentially be delivered by letter. Genetic counselors would only be needed when a result was found that could affect the health of offspring.

Our results on mental health utilization do not rule out the possibility of mild increases in stress following screening that are

not severe enough to cause women to seek treatment. It is important to note that barriers to accessing mental health care were relatively low for the insured population under study, who were all receiving regular medical care.

CONCLUSIONS

This preliminary study shows little evidence of harms of ECS, either during the period between screening and receiving results or after receiving negative screening results. Although future studies should continue to explore the possibility of harms of screening, particularly for non-White and low-income populations who were underrepresented in the current sample, these results may reassure health insurance coverage decision makers considering implementation of ECS programs. ■

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TABLE 4. Pregnancy-Related Service Use 5 Years Before and at Any Time After Study Entry Among Low-Risk Women With Pregnancies of at Least 6 Months

Type of utilization	Expanded carrier screening		OR	95% CI	P
	(n = 61)	Usual care (n = 98)			
Pregnancy ^a before study entry	35%	34%	N/A		N/A
Pregnancy ^a following study entry	25%	24%	N/A		N/A
Among pregnancies (n)	67	106			
First trimester screening uptake ^b					
Prestudy	88%	90%			
Post study	81%	93%	0.43	0.006-32.8	.49
Second trimester screening uptake ^c					
Prestudy	85%	87%			
Post study	70%	84%	0.52	0.011-25.0	.54
Screening/diagnostic test refusals					
Prestudy	13%	13%			
Post study	15%	9%	1.80	0.027-118	.61
Other relevant genetic testing					
Prestudy	8%	5%			
Post study	4%	9%	0.24	<0.001-115	.43

AFP, α-fetoprotein; AFP4, α-fetoprotein 4; MSAFP, maternal serum α-fetoprotein; MSAFP4, maternal serum α-fetoprotein 4; N/A, not applicable; NIPT, noninvasive prenatal testing; OR, odds ratio.

^aSix months or longer in duration and continuous health plan membership during entire pregnancy.

^bIncludes first trimester screen and NIPT.

^cIncludes quad screen, AFP4, MSAFP4, AFP, and MSAFP.

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