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Evaluating the efficacy of three carrier screening workflows designed to identify at-risk carrier couples

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Abstract

Objective: To evaluate the efficacy of three different carrier screening workflows designed to identify couples at risk for having offspring with autosomal recessive conditions.

Methods: Partner testing compliance, unnecessary testing, turnaround time, and ability to identify at-risk couples (ARCs) were measured across all three screening strategies (sequential, tandem, or tandem reflex).

Results: A total of 314,100 individuals who underwent carrier screening were analyzed. Sequential, tandem, and tandem reflex screening yielded compliance frequencies of 25.8%, 100%, and 95.9%, respectively. Among 14,595 couples tested in tandem, 42.2% of females were screen-negative, resulting in unnecessary testing of the male partner. In contrast, less than 1% of tandem reflex couples included unnecessary male testing. The median turnaround times were 29.2 days (sequential), 8 days (tandem), and 13.3 days (tandem reflex). The proportion of ARCs detected per total number of individual screens were 0.5% for sequential testing and 1.3% for both tandem and tandem reflex testing.

Conclusion: The tandem reflex strategy simplifies a potentially complex clinical scenario by providing a mechanism by which providers can maximize partner compliance and the detection of at-risk couples while minimizing workflow burden and unnecessary testing and is more efficacious than both sequential and tandem screening strategies.

Highlights

What's already known about this topic?

- Studies have explored barriers to carrier screening and follow up partner testing to identify at-risk couples. However, to date, no one has explored the efficacy of different carrier screening workflows.

Ben-Shachar and Johansen Taber are co-senior authors.

What does this study add?

- This study highlights how providers could maximize the utility of carrier screening in identifying at-risk couples based on the screening strategy utilized.

1 | INTRODUCTION

Carrier screening is offered to individuals and couples to identify those at risk of having children with certain recessive and X-linked genetic conditions. Over the last decade, more than a million individuals have undergone pan-ethnic expanded carrier screening (ECS), that is, screening for a large number of conditions regardless of one's ethnic background or family history.[1,2] ECS is one of the carrier screening strategies supported by the American College of Obstetricians and Gynecologists (ACOG),[3] and has been shown to more effectively identify carriers and affected pregnancies across all ethnicities than currently recommended ethnicity-based screening.[3,4] Approximately 1 in 300 pregnancies in the United States is expected to be affected with a serious genetic condition and 1 in 22 couples is at risk of having an affected child.[5]

To provide comprehensive risk information to patients pursuing ECS and identify at-risk couples (ARCs), it is critical to obtain results from both partners. Results enable couples to make reproductive decisions based on their personal values and preferences.[3,6] ARCs can pursue options, such as in-vitro fertilization with preimplantation genetic testing, use of an egg or sperm donor, prenatal diagnostic testing, adoption, and/or pregnancy termination.[6] Advanced knowledge can also help individuals and providers develop a pregnancy management plan, decrease time to diagnose an affected child, improve perinatal outcomes, and facilitate education about special care needs after birth.[3]

The most common way to identify ARCs is via "sequential screening," in which the female partner is screened first and, if found to be a carrier,[6,7] the partner is screened for the condition(s) for which the female was found to be a carrier (Figure 1). In current practice, this commonly necessitates a subsequent visit to a provider for collection of the partner's sample, such that the time to receive a combined couple report is often more than double the time it takes to receive an individual report.[3,7,8] The need for a secondary sample submission has been found to significantly reduce subsequent partner screening, and ultimately ARC detection, primarily due to workflow challenges and lack of follow-up of male partners.[7] In one study, only 38% of male partners followed-up with screening.[7] Lack of male partner follow-up diminishes the ability of ECS to provide clinically actionable results, underscoring the need for mechanisms to efficiently gather the male partner's sample and decrease provider workload.

Alternatively, both partners' samples can be collected and tested simultaneously with "tandem screening" (Figure 1). This strategy is recommended if there are time constraints for decisions about prenatal diagnostic evaluation.[8] Tandem screening addresses the inherent time delays of sequential screening and the challenge of arranging for a second clinic visit to collect the partner's sample. However, it results in needless testing of partner samples for which no reproductive risk was identified in the other partner.[7]

"Tandem reflex" screening is a novel strategy to limit unnecessary partner testing by collecting both partners' samples in tandem, but testing the second partner's sample only if the first partner was found to be a carrier of an autosomal recessive condition (Figure 1). In this study, we evaluated the overall efficacy of a pilot tandem reflex screening program in comparison to traditional sequential and tandem screening strategies by examining partner compliance, unnecessary testing, turnaround time, and ARC detection, as well as the efficiency of healthcare utilization, associated with each strategy. We anticipated that tandem reflex screening would be the most efficient screening solution.

2 | METHODS

2.1 | Patient population and carrier screening

We retrospectively analyzed deidentified data from samples tested using the Foresight® Carrier Screen (Myriad Women's Health), which included up to 176 genes,[5,9] over a 25-month period. The methodology of the Foresight Carrier Screen has been previously described in Hogan et al.[5] The panel prioritizes prevalent diseases that are profound and severe as described in Beauchamp et al.[9] and Arjunan et al.[10] Patients and couples considered to be "at risk" were those with variants that were interpreted as being likely pathogenic or pathogenic via the American College of Medical Genetics and Genomics Criteria.[11] The at-risk calculations accounted for known disease-specific variant combinations that influence pathogenicity (e.g., a couple in which both partners were silent carriers for alpha thalassemia and therefore not at risk of an affected child were not counted as an ARC). Patients were excluded if they were under age 18 years, opted out of being involved in research at Myriad Women's Health, were from New York state, or indicated that they were egg/sperm donors. After exclusions, a total of 314,100 patients were included in analysis, including 35,899 total couples. For those screened sequentially, a couple-based report was issued when a provider indicated that the patient's partner had been screened. Patients and providers could also request a couple-based report after both partners had been screened. Couple-based reports were automatically generated following tandem and tandem reflex screening. Clinical and demographic data were obtained from the provider-completed test requisition form and included date of birth, ethnicity, and pregnancy status. This study was designated as exempt from institutional review board (IRB) oversight by Advarra IRB (Pro00042075).

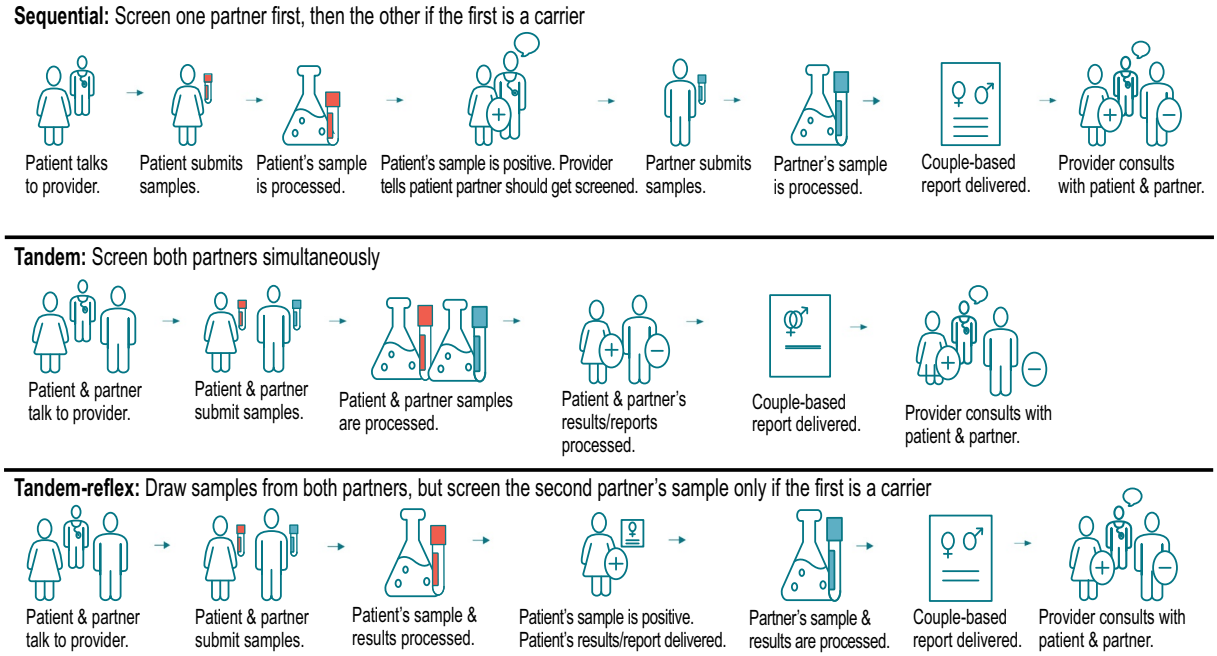

FIGURE 1 Overview of different carrier screening strategies [Colour figure can be viewed at wileyonlinelibrary.com]

2.2 | Efficacy of screening strategies

The primary outcome of this study was to determine the efficacy of the sequential, tandem, and tandem reflex strategies. This outcome was evaluated by measuring impact on partner testing compliance, unnecessary male testing, turnaround time, and ability to identify ARCs across all screening strategies.

Partner compliance was defined as the testing of the male partner when the female was identified as a carrier (screen-positive) for one or more autosomal recessive conditions (Figure 2). To calculate the frequency of compliance, the total number of compliant coupled partners was divided by the total number of females screening positive for an autosomal recessive condition, irrespective of whether they had an identified male partner (Figure 2). For sequential screening, we could not verify partner identity for some screened males because not all males were linked to a female screen. Therefore, we calculated an upper bound of compliance by assuming that all males were screened as a result of having a screen-positive female partner. For such patients, we included a 20-day lag time between females and males to allow sufficient time for sequential screening to take place so that both partners would be captured (i.e., both males and females were sampled over 24 months, but respective start and end dates were staggered by 20 days).

Unnecessary male testing for each screening strategy was defined as a male receiving testing after his female partner initially screened negative for all autosomal recessive conditions screened (Figure 2). For testing to qualify as unnecessary, three conditions had to be met: (1) the female partner screened negative for all autosomal recessive conditions; (2) the female partner had an identified male partner that was also screened; and (3) the female partner had to receive her screening either before or tandemly with her male partner (females who were screened *following* a completed male partner screen were excluded). To calculate the frequency of unnecessary testing, the total number of females meeting the three conditions above was divided by all males that were tested following (or in tandem with) a female screen.

Turnaround time for couples was defined as the time difference (in days) between start of laboratory processing of the first partner (irrespective of sex) and the reporting of couple-based report results to the provider.

2.3 | Impact of screening strategy on ARC detection

Couples were counted as ARCs if both partners were carriers for the same autosomal recessive disease (i.e., excluding X-linked conditions). To control for biases that panel size could have on disease-wide carrier frequency, we limited ARC analyses to individuals screened for all autosomal conditions on the Foresight 176-gene panel and couples in which the first partner screened was female (or tandemly tested with a male partner). We calculated the number of observed ARCs divided by the total patients screened rather than the total number of couples screened to incorporate both the impact of compliance and unnecessary testing on ARC detection. Additionally, provider burden was calculated as percentage of expected provider follow-up coordination as a function of number of female screens (assumes one provider

FIGURE 2 Efficacy of screening strategies

consultation for follow-up per carrier identification and per ARC identification).

2.4 | Modeling the impact of screening strategies on healthcare utilization

The secondary outcome of this study was to determine the impact of the three partner screening strategies on healthcare utilization. For this outcome, a simulation modeling approach was used to compare the impact of the different screening strategies on healthcare utilization (see Methods in Supporting Information Material).

2.5 | Data analysis

All pairwise comparisons of partner screening strategies, including turnaround times, were analyzed via a two-sided Mann–Whitney *U* test. Differences in proportion of ethnicities screened by each strategy were analyzed using a χ^2 test. For assessing significance, an α of 0.05 was used for all statistical tests. All calculations were performed using Python version 3.6.8.

3 | RESULTS

3.1 | Patient population

After exclusion criteria were applied, a total of 314,100 individuals (including 35,899 total couples) who underwent sequential ($N = 280{,}090$), tandem ($N = 29{,}190$), or tandem reflex ($N = 4820$) carrier screening workflows were analyzed. Demographics of patients that underwent each screening strategy are summarized in Tables 1 and S1. The ethnicity distributions across all screening strategies were significantly different from one another ($p < 0.05$, Table 1). Between 26% and 57% of the females across the screening strategies were pregnant when they received screening (Table 1).

3.2 | Efficacy of screening strategies

3.2.1 | Compliance

Partner compliance refers to screening of the male partner when the female partner is identified as a carrier (screen-positive) for one or

TABLE 1 Characteristics of patients[a] who underwent expanded carrier screening ($n = 314{,}100$)

Characteristic	Sequential ($n = 280{,}090$)	Tandem ($n = 29{,}190$)	Tandem reflex ($n = 4820$)
Age, *n* (%)			
18–24	32,162 (11%)	598 (2%)	151 (3%)
25–29	55,546 (19%)	3,054 (10%)	601 (12%)
30–34	93,649 (33%)	9,802 (33%)	1,912 (39%)
35–39	69,220 (24%)	9,969 (34%)	1,504 (31%)
40 and above	29,513 (10%)	5,767 (19%)	652 (13%)
Self-reported ethnicity, *n* (%)			
Mixed/other Caucasian	71,652* (25%)	5,456* (18%)	1,063 (22%)
Unknown	60,382* (21%)	6,825* (23%)	1,449 (30%)
Northern European	40,238* (14%)	7,377* (25%)	945 (19%)
Hispanic	31,726* (11%)	1,326* (4%)	257 (5%)
African or African American	29,953* (10%)	1,456 (4%)	249 (5%)
Ashkenazi Jewish	13,004* (4%)	1,490* (5%)	185 (3%)
East Asian	10,163* (3%)	2,201* (7%)	266 (5%)
South Asian	8,465 (3%)	1,266* (4%)	159 (3%)
Southern European	4,590* (1%)	572* (1%)	129 (2%)
Southeast Asian	3,996 (1%)	408 (1%)	59 (1%)
Middle Eastern	3,754* (1%)	621* (2%)	42 (0%)
French Canadian or Cajun	1,068 (0%)	105 (0%)	14 (0%)
Native American	646* (0%)	49 (0%)	1 (0%)
Pacific Islander	398 (0%)	34 (0%)	2 (0%)
Finnish	55 (0%)	4 (0%)	0 (0%)
Pregnancy status, *n* (% of all females)			
Pregnant	129,508 (56.8%)	3,865 (26.5%)	1,016 (32.9%)

[a]Includes females/males without a testing partner.

*Significant difference ($p < 0.05$) when compared to the tandem reflex screening strategy.

more autosomal recessive condition(s). Out of 70,429 females who screened positive via the sequential screening strategy, 18,166 had a male partner screened, yielding a compliance frequency of 25.8% (Figure 3A). Because we cannot assess partner status for some screened males (i.e., 32,498 total males outside of tandem and tandem reflex were unpartnered), we calculated an upper bound of compliance by assuming that these unpartnered males were screened following a screen-positive female. This yielded an upper bound compliance estimate of 71.9% for sequential screening. Out of 1762 total females who screened positive using tandem reflex, 1690 (95.9%) had a male partner screened, as some males opted out of continuing screening. This represented a fourfold increase in compliance for tandem reflex relative to sequential screening (Figure 3A) and a 1.3-fold increase when comparing to the upper bound estimate for sequential screening. As expected for tandem screening, compliance was 100%––all 8432 females who screened positive using tandem had a male partner screened (Figure 3A).

3.2.2 | Unnecessary testing

Unnecessary testing refers to screening of the male partner after the female partner has already screened negative. Among females screened using the tandem strategy, 42.2% (6163/14,595) were found not to be carriers for any autosomal recessive conditions. Because the tandem strategy tests all male partners regardless of the female's result, the 6163 male partners screened by the tandem strategy represented unnecessary tests (Figure 3B). The frequency of unnecessary male testing for the sequential and tandem reflex strategies was 3.2% and 0.6%, respectively, as some male partners

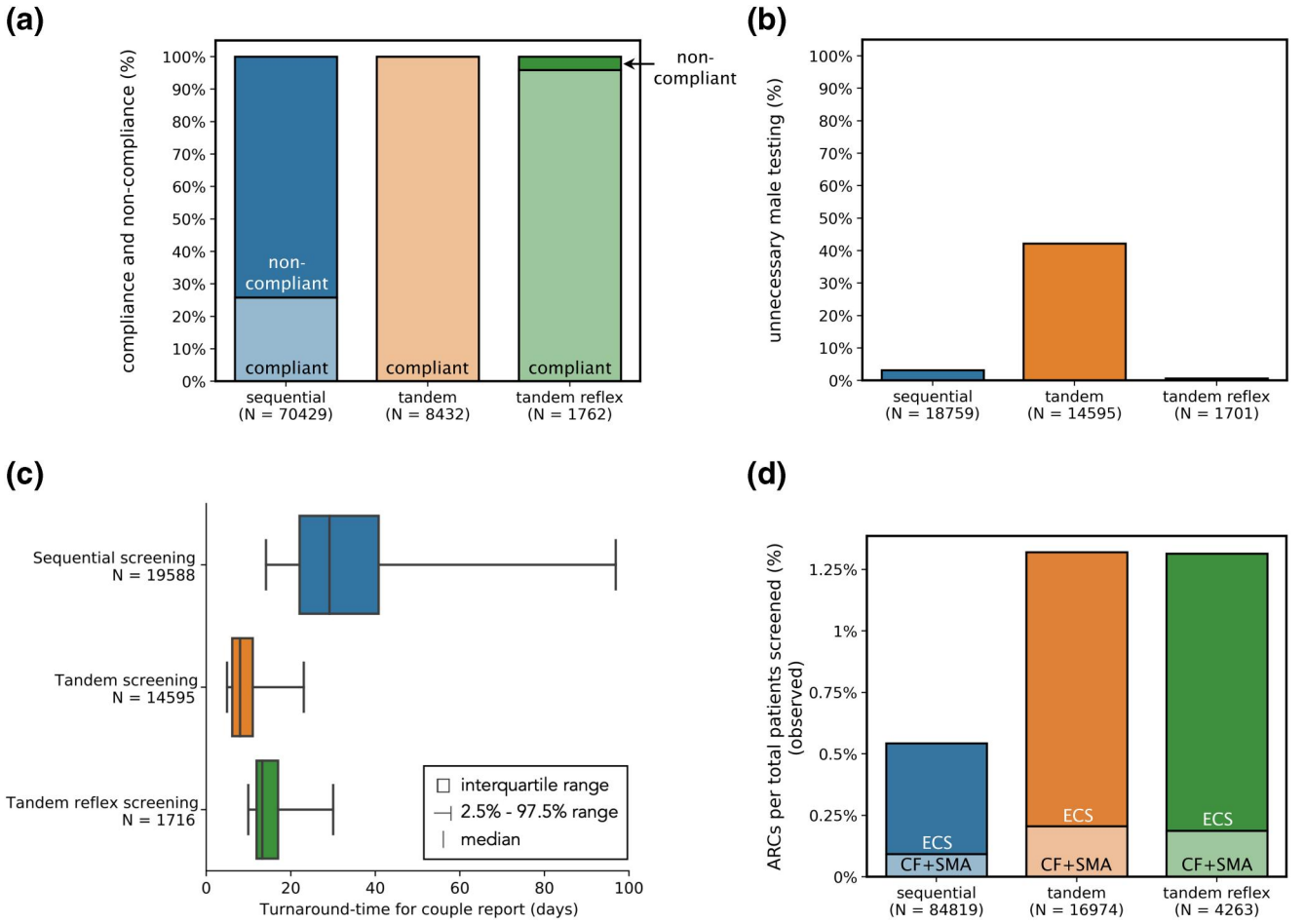

FIGURE 3 Impact of tandem reflex strategy on ECS efficacy. (A) Partner testing compliance, defined as the proportion of male partners who were (compliant) or were not (noncompliant) screened when the female partner was identified as a carrier of a recessive disease (screen-positive). (B) The frequency of unnecessary male testing, defined as the proportion of male partner samples screened after the female partner was first identified as screen-negative. (C) The turnaround time from when the first test was ordered to receipt of the couple report. The total number of couples analyzed for each screening strategy is indicated. Couple-based turnaround time can only be calculated in cases of male partner compliance. (D) ARC detection efficacy, defined as the proportion of ARCs detected as a function of total individual patients screened (only individuals/couples screened on the 176-gene panel are included in calculations). ARC, at-risk couple; ECS, expanded carrier screening; CF, cystic fibrosis; SMA, spinal muscular atrophy [Colour figure can be viewed at wileyonlinelibrary.com]

elected to continue their screening even though their female partner screened negative (Figure 3B).

3.2.3 | Turnaround time

Turnaround time refers to the time it takes for a couple to receive results after screening has been ordered. Couples screened via the sequential strategy had a median turnaround time of 29.2 days for a couple-based report (Figure 3C). Couples screened in tandem had a median turnaround time of 8.0 days (Figure 3C), representing a significant 72.6% reduction in turnaround time ($p < 0.05$) compared to sequential screening. Couples screened via the tandem reflex strategy had a median turnaround time of 13.3 days (Figure 3C), representing a statistically significant 54.5% reduction in turnaround time compared to sequential screening ($p < 0.05$).

3.2.4 | Carrier and ARC identification

As cystic fibrosis (CF) and spinal muscular atrophy (SMA) are the only conditions recommended by ACOG for pan-ethnic screening, we assessed the frequency of patients identified as carriers and ARCs when screening for CF and SMA only by each screening strategy, and compared such frequencies to those identified by a 176-gene ECS panel (Table 2). The carrier frequencies for CF and SMA were 6.9%, 8.3%, and 7.1% for the sequential, tandem, and tandem reflex strategies, respectively. In contrast, the panel-wide carrier frequencies were 57.4%, 60.6%, and 59.0%, respectively, for patients that underwent ECS (Table 2). The percentage of CF and SMA ARCs identified per total number of individual screens were 0.1%, 0.2%, and 0.2% for sequential, tandem, and tandem reflex, respectively. In contrast, the percentage of ARCs identified were 0.5%, 1.3%, and 1.3% respectively for patients that underwent ECS (Table 2; Figure 3D). Taken together, ECS detected more than

TABLE 2 Carrier frequencies, at-risk couple detection efficacy, and estimated provider burden stratified by screening strategy and disease panel[a]

	CF/SMA female carrier frequency[b]	CF/SMA ARC detection efficacy[c]	CF/SMA provider burden[d]	ECS female carrier frequency[b]	ECS ARC detection efficacy[c]	ECS provider burden[d]
Sequential	6.9%	0.1%	7.0%	57.4%	0.5%	58.0%
Tandem	8.3%	0.2%	0.4%	60.6%	1.3%	2.6%
Tandem reflex	7.1%	0.2%	0.3%	59.0%	1.3%	2.1%

Abbreviations: ARC, at-risk couple; CF, cystic fibrosis; ECS, expanded carrier screening; SMA, spinal muscular atrophy.

[a]Autosomal recessive conditions only.

[b]Carrier frequencies are calculated as the percentage of females that screened positive per number of females screened (only females screened on the 176-gene panel are included in calculations).

[c]ARC detection efficacy defined as the proportion of ARCs detected as a function of total individual patients screened (only individuals/couples screened on the 176-gene panel are included in calculations; see Figure 3).

[d]Provider burden calculated as percentage of expected provider consultations as a function of number of female screens. This assumes one provider consultation per carrier identification and per ARC identification for the sequential strategy and one provider consultation per ARC identification for the tandem and tandem reflex strategies.

sevenfold higher carriers and more than fivefold higher ARCs compared to screening for CF and SMA alone. For patients that underwent ECS, ARCs were identified for 89 additional genes other than CF and SMA across all three screening strategies (Table S2).

An additional consideration in ARC detection is the required provider follow-up needed for partner testing and results disclosure. For sequential screening, providers must follow-up to coordinate next steps with individual carriers (including the discussion of partner screening) and with each identified ARC, while with tandem and tandem reflex screening, providers need only to coordinate results disclosure with ARCs. In this study, sequential screening would have resulted in a provider burden of 7.0% for CF/SMA-only screening and 58.0% for ECS. For tandem screening and tandem reflex screening, the provider burden was close to their respective frequencies of ARC detection, that is, 0.4% for CF/SMA and 2.6% for ECS with tandem screening, and 0.3% for CF/SMA and 2.1% for ECS with tandem reflex.

3.3 | Efficiency of healthcare utilization

To compare the efficiency of healthcare utilization for each screening strategy, we examined the number of noneffective tests (due to either partner noncompliance or unnecessary screens) for each screening strategy. We used a modeling approach to demonstrate the impact of noneffective tests for different partner screening implementation scenarios. Simulation of widespread partner screening of 50,000 total screens resulted in 21,551 (43.1%) and 21,066 (42.1%) noneffective tests for the sequential and tandem screening strategies, respectively (Figure 4A). In contrast, tandem reflex screening resulted in only 1,359 (2.7%) noneffective tests, a more than 15-fold reduction when compared to both the sequential and tandem strategies.

We also modeled the number of autosomal recessive ARCs identified using the 176-gene ECS panel, while also controlling for known differences in the ethnicity distribution of patients tested across each strategy. Simulations showed that ARC detection by the tandem reflex strategy was 1.3-fold higher compared to the tandem strategy (1.5% vs. 1.2%, $p < 0.05$) and threefold higher compared to the sequential strategy (1.5% vs. 0.5%, $p < 0.05$; Figure 4B). Simulation of 50,000 female screens resulted in over 100 additional ARCs captured by tandem reflex screening compared to tandem screening (tandem reflex: 749 ARCs, tandem: 607 ARCs, $p < 0.05$) and nearly 500 additional ARCs compared to sequential screening (sequential: 273 ARCs, $p < 0.05$; Figure 4C).

4 | DISCUSSION

Efficient strategies for enabling partner carrier screening are needed to maximize ARC detection and clinical utility. In this study, we demonstrated that a tandem reflex screening strategy was the most effective of those evaluated for identifying ARCs, as it resulted in high partner compliance, low unnecessary testing, and a short turnaround time.

The sequential screening strategy had a frequency of compliance that was nearly fourfold lower than the tandem and tandem reflex strategies (25.8% vs. 100% and 95.9%, respectively). Although the reasons for noncompliance in the sequential screening group were not collected here, we can surmise several. Partner samples can be difficult to obtain, often requiring the partner to visit a laboratory/clinic that may be outside of their insurer.[7] Male partners have also reported the belief that results would not impact pregnancy management, not wanting to know their carrier status, and concern about the cost and insurance coverage of screening.[12,13] A recent study's comparatively high frequency of compliance (77%) was attributed to the center's

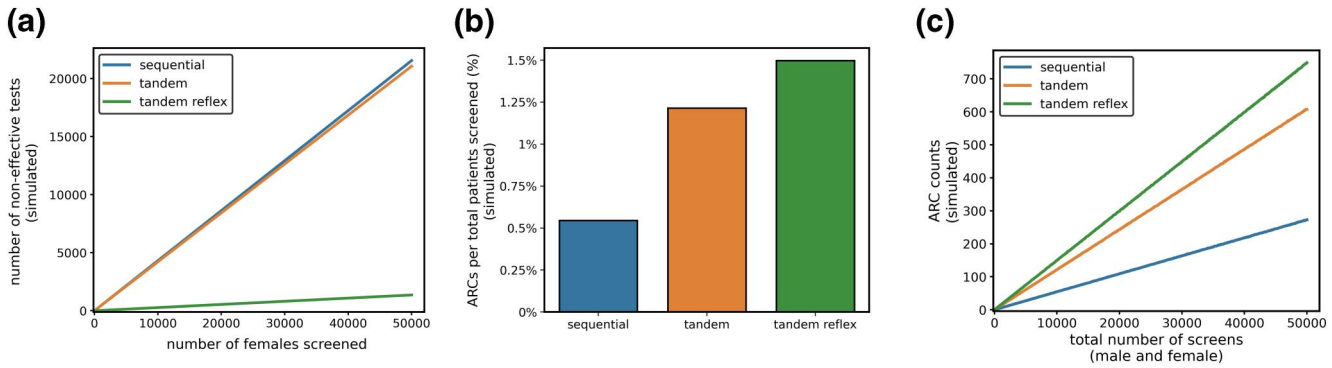

FIGURE 4 Modeled impact of screening strategies on healthcare utilization. (A) Simulated number of noneffective tests as a function of the number of females screened. (B) The simulated frequency of at-risk couples (ARCs) detected per total patients screened for autosomal recessive conditions on the 176-gene panel for each screening strategy, while also correcting for differences in ethnicity distribution in patient cohort across screening strategies. (C) The simulated number of ARCs detected by each screening strategy as a function of total patients screened on the 176-gene panel [Colour figure can be viewed at wileyonlinelibrary.com]

protocol for arranging posttest counseling appointments, drawing the partner's blood on the day of the follow-up visit, and offering free or reduced-cost testing in many cases.[12] In our study, high compliance in the tandem and tandem reflex groups translated into a higher percentage of identified ARCs compared to the sequential group, a result additionally demonstrated by modeling data.

This study also demonstrated the ability of the tandem reflex approach to reduce unnecessary screening. In contrast to the more than 40% of males screened by the tandem strategy whose partners had already screened negative, almost no males were screened unnecessarily using the tandem reflex strategy. When evaluating the strategies as a function of noneffective screens—which combines the effects of both noncompliant and unnecessary testing—the tandem reflex strategy resulted in a 15-fold reduction in noneffective tests. This illustrates that tandem reflex is a more efficient screening strategy overall than sequential or tandem screening, thereby maximizing efficient healthcare utilization. Cost-effectiveness analyses that characterize the extent of efficiency will be important as large-scale partner screening programs are implemented.

A short turnaround time is critical when a couple is pregnant and at a gestational age at which decisions about diagnostic testing or other interventions must be made without delay. ACOG, therefore, recommends concurrent screening of both partners if such time constraints exist.[3] The tandem reflex strategy is consistent with this recommendation, with a median turnaround time more than half that of sequential screening (13.3 days compared to 29.2 days). These results for sequential screening are similar to those observed in other studies; in a study in which partners had to return to the clinic for sample collection, the time to generate a couple-based report was over a month (33.9 days).[7] Patients have reported anxiety waiting for partner screening results[14,15] and a reduction in turnaround time could reduce such anxiety, though additional research may be needed to test this hypothesis.

Pan-ethnic carrier screening has traditionally been limited to CF and, more recently, SMA. However, ECS identifies ARCs for many conditions that are equally as or more severe than CF and SMA.[10,16,17] An additional consideration is the time commitment required for provider follow-up for both partner testing and results disclosure, particularly for ECS panels that may result in a higher number of positive results than screening for only CF or SMA. For sequential screening, providers must coordinate follow-up for individual carriers to discuss partner screening and for ARCs to communicate results, whereas for tandem and tandem reflex screening, providers need only coordinate follow-up with ARCs. The tandem reflex strategy reduced the number of patients with whom providers must follow up by 3.3-fold, even when dozens of conditions are included in the panel, versus sequential screening for only CF and SMA. This reduction in provider burden could additionally contribute to the potential healthcare cost reductions realized by the increased compliance and reduced unnecessary testing seen with tandem reflex screening, though additional studies are needed to explore this hypothesis.

4.1 | Limitations

This study was primarily based on female/male couples pursuing a pregnancy and is not generalizable to situations in which couples use donor gametes or females pursue a pregnancy without a male partner. We could not account for all partners in the sequential strategy because some reports did not reflect results of both members of the reproductive couple. It is also possible that some of these individuals were utilizing gamete donors, which would not result in a couple-based report. Reasons for noncompliance were not collected, as all data were obtained in the course of routine clinical testing. It is possible that partner compliance is dependent on certain patient demographics that were different across the three screening strategies; for example, those in the sequential screening group tended to be younger and were more likely to be pregnant when screened compared to those in the tandem and tandem reflex groups. Further research is needed to determine

whether these factors appreciably impact partner compliance. Additionally, due to data deidentification, we could not identify the exact reasons for the small number of unnecessary tests in the tandem reflex group, although we speculate this number reflected the ability of partners to request screening even when their partner had already screened negative.

5 | CONCLUSIONS

Our study demonstrates that the tandem reflex screening strategy has the highest efficacy, when all factors are combined, compared to sequential and tandem screening and is the most efficient way for clinics to implement recommended carrier screening resulting in high partner screening compliance, limited unnecessary partner screening, timely results for a couple-based report, and high identification of at-risk couples.

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CONFLICT OF INTERESTS

All authors were employees of Myriad Women's Health or Myriad Genetics, Inc., at the time the research for this study was conducted and received salary and stock options.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study have been completely reported in this manuscript and shared in the tables, figures, and supplementary material.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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