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ARTICLE

Choosing an expanded carrier screening panel: comparing two panels at a single fertility centre

BIOGRAPHY

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KEY MESSAGE

Carrier rates and carrier couple rates increase as expanded carrier screening panels include more disorders and mutations. These rates, however, vary based on self-reported ethnicity. Preconception carrier screening of a diverse ethnic population benefits from a more broadened and comprehensive expanded carrier screening panel.

ABSTRACT

Research question: What are the factors contributing to similarities and differences in carrier rates between two expanded carrier screening (ECS) panels?

Design: Retrospective cross-sectional study. A total of 7700 infertility patients who underwent ECS from one of two genetic testing laboratories (Panel A or Panel B) using a genotyping microarray were included in the study. Individuals presenting to the Centre between June 2013 and July 2015 underwent screening via Panel A. Those presenting between August 2015 and April 2017 underwent screening via Panel B. Self-reported ethnicity was recorded. Panel content, carrier rates for the overall study population and for comparable self-reported ethnicities, carrier couple rates, and the top 10 identified disorders were compared.

Results: Of 4232 individuals screened by Panel A, 1243 were identified as carriers (29.4%). Panel B identified 1503 carriers among the 3468 (43.3%) participants ($P < 0.0001$). Carrier couple rate also varied between panels (1.2% versus 3.1%; $P = 0.0017$). A total of 311 disorders covering 2746 mutations were observed across the two ECS panels, with 372 (13.5%) shared mutations. Carrier rates did not differ for the shared mutations overall and across ethnicities. Significant differences were observed when comparing unique content in the overall population ($P < 2\ .2 \times 10^{-16}$) and across ethnicities ($P < 2.2 \times 10^{-16}$ to 0.0010).

Conclusions: Carrier rates in the overall population and across ethnicities vary widely based on panel content, and highlight the need to expand panel content as well as incorporate preconception carrier screening coupled with genetic counselling into routine assisted reproduction practice.

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Declaration: SLB was employed by Recombine from January 2014 to May 2016 as a research coordinator in the R&D division. AG was employed by Recombine from June 2015 to May 2017 as a genetic counsellor providing clinical support to patients receiving ECS testing. Neither of the authors were directly involved with panel or commercial development.

KEYWORDS

Carrier rate
Ethnicity-based carrier screening
Expanded carrier screening
Preconception genetic screening
Preimplantation genetic testing

INTRODUCTION

In fertility centres across the USA, carrier screening is rapidly shifting from traditional ethnicity-based screening to expanded carrier screening (ECS) as a result of both demographic changes and technological advances in the past decade. The US population has become increasingly heterogeneous, with growing proportions of individuals reporting mixed ancestry and increasing numbers of mixed ethnicity couples (*US Census Bureau, 2010; Nazareth et al., 2015*). As a result, self-reported ancestries may not reflect an individual's true genetic makeup and is bound to result in missed carrier status for mutations that are outside of the recommendations for ethnicity-based screening. Ethnicity-agnostic screening using an ECS panel eliminates the issues of inaccurate or incomplete patient self-reporting. In addition to demographic changes, the development and implementation of advanced genomic technologies now allow for multiplexed platforms with the ability to screen thousands of mutations at one time with a single sample from the patient at an exponentially shrinking cost.

As ECS use has grown and taken a larger role in preconception and prenatal counselling, several professional societies have released recommendations regarding their development and implementation. Initial recommendations from the American College of Medical Genetics and Genomics acknowledged the increased use of ECS in clinical settings, and recommended guidelines on panel design (*Grody et al., 2013*). A subsequent joint statement from the American College of Medical Genetics and Genomics, American Congress of Obstetricians and Gynecologists, National Society of Genetic Counselors, Perinatal Quality Foundation, and Society for Maternal Fetal Medicine supported the addition of ECS to the repertoire of tools available for genetic screening; however, it did not seek to reform or replace the existing practice guidelines of each professional society (*Edwards et al., 2015*). More recently, a Committee Opinion on carrier screening from American Congress of Obstetricians and Gynecologists suggested that ECS, ethnicity-based screening and pan-ethnic screening are all acceptable strategies with the caveat that the offering should be consistent within a practice such that all patients are provided the same care (*Rink et al., 2017*). Although many professional societies have shown support for the use of ECS, these statements do not include strict guidelines establishing which disorders or mutations should be included, but rather a list of criteria that disorders should meet before being included in a screening panel.

With no oversight or unified professional guidance, genetic testing laboratories have developed ECS panels that vary greatly in scope and include disorders that have variable penetrance as well as health ramifications (*Rose, 2015*). Recent analysis of 16 different ECS panels revealed that the number of included diseases ranged from 41 up to nearly 1800 (*Chokoshvili et al., 2017*). Furthermore, only three disorders were shared among all 16 (cystic fibrosis, maple syrup urine disease 1b and Neimann–Pick disease), all of which varied greatly in the mutations included. A recent study suggested more specific guidelines for selecting disorders and associated mutations appropriate for ECS, and subsequently evaluated panels from six commercial companies based on these criteria (*Stevens et al., 2017*). Only 26.7% of each panel, on average, met their criteria, whereas the rest should not be included. With several competing options for ECS panels, physicians are left with an often confusing choice of which panel is appropriate for their patient population.

This study compared two ECS genotyping panels from two different genetic testing laboratories widely used in the USA, offered to patients at our single, large-volume, academic fertility centre. The ECS panels were offered routinely to patients as standard of care during two distinct time periods. We investigate how the panels differ from each other and compare carrier rates in the overall population and in different ethnic populations in order to better define factors to be considered when choosing a panel that will best benefit patients. We also compare carrier couple rates, where both partners carry mutations for the same disorder. Here, we provide data that can help inform physician choices for ECS panels most appropriate for their patient population.

MATERIALS AND METHODS

Participants

The ECS results were reviewed retrospectively for patients seen at Northwell Health Fertility (Manhasset, NY, USA) between June 2013 and January 2017. Screening through one of two genetic testing laboratories was offered to all patients at the time of their initial consultation. The ECS panel offered was based on the time the patient presented to the Centre. Panel A (Counsyl, San Francisco, CA, USA) was used from June 2013 to July 2015. Panel B (Recombine, Livingston, NJ, USA) was used from August 2015 to April 2017. At the time of providing a blood sample, the patients completed a requisition form from the vendor on which the patient self-reported their ethnicity.

All study procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. The Northwell Health Institutional Review Board reviewed and approved this study on 28 March 2017 (IRB reference number: 17-0145).

ECS panel description

Blood samples from each patient were tested for clinically significant mutations via microarray using one of two commercially available ECS panels. Panel A is composed of 401 variants in 102 genetic diseases and Panel B is composed of 2717 variants in 307 genetic diseases. For both panels, additional testing for determining the number of CGG repeats in the 5′-UTR of FMR1 (Fragile X Syndrome) and the copy number of exon 7 in SMN1 (Spinal Muscular Atrophy) was carried out.

Comparing ECS panels

First, we identified disorders included on both panels. Then, we categorized genotyped variants into three groups: group 1: mutations included in both panels; group 2: additional mutations for shared disorders included on only one panel; and group 3: mutations associated with disorders only screened on one panel. The carrier frequency of the overall panel and for each mutation group was calculated for both laboratories.

For each panel, the 10 most common disorders were calculated and compared to determine whether number of carriers identified by each panel differed, and whether the difference was attributable to the additional mutations included

in one or both of the panels for each disorder, if applicable.

In cases in which both partners were tested, their ECS results were compared with each other to determine if they were both carriers for the same disorder (carrier couples). Only autosomal recessive disorders were included in this analysis. For each carrier couple, it was assessed if both or only one of the panels would have identified them.

Comparing ECS panels based on ethnicity

Self-reported ethnicity was used to investigate differences in carrier rate across ethnicities. Each testing company offers a different selection of ethnicities. Panel A ethnicity options include the following: African or African American; Ashkenazi Jewish; East Asian; French Canadian or Cajun; Hispanic; Middle Eastern; Mixed or other Caucasian; Native American; Northern European; Pacific Islander; South Asian; Southeast Asian; Southern European; and unknown/not reported. Panel B ethnicity options include the following: African; East Asian; European; French Canadian; Jewish; Latin American; Mediterranean; Middle Eastern; Native American; Other; South Asian; Southeast Asian; unreported. Additionally, Panel A reports one ethnicity for each patient, whereas Panel B reports all ethnicities selected on their requisition forms.

Where possible, a straightforward comparison was made between patients with similar ethnicity choices. If no comparable ethnicity was offered by one of the panels, or the sample size was below 50 for the ethnicity grouping, patients who self-reported that ethnicity were excluded from analysis based on ethnicity, e.g. 'Pacific Islander' from Panel A. Participants selecting multiple ethnicities on Panel B were placed in a larger ethnic categorization if possible, e.g. selection of 'European' and any other ethnicity from Panel B was categorized as 'mixed/other Caucasian' to match Panel A. To compare the 'Ashkenazi Jewish' population from Panel A to an equivalent population from Panel B, individuals that selected either 'Jewish' or both 'European' and 'Jewish' were included, as individuals with Jewish relatives originating from Europe are typically of Ashkenazi Jewish decent (*ACOG Committee on Genetics, 2015*). Additionally, up to 95% of Americans reporting Jewish descent are Ashkenazi (*Egan et al., 1996; Driscoll et al., 2017*). Individuals who selected 'Jewish' and at least one other category were excluded from the comparison with Panel A's 'Ashkenazi Jewish' subpopulation.

Statistical analysis

Two-tailed unpaired t-tests were used to assess differences in age between the two panels. Chi-squared and Fisher's exact tests were used to assess differences in carrier rates. A cut-off value of $P \leq 0.05$ was considered significant in all cases. All analyses were carried out using R (v 3.3.3) (*R Core Team, 2017*).

RESULTS

A total of 7700 individuals who had carrier screening from one of the two ECS panels at one fertility centre were included in the study. A total of 4232 (55.0%) participants underwent testing with Panel A and 3468 (45.0%) underwent testing with Panel B. Mean age of participants was compared by gender and was similar in the two groups. The mean female age for Panel A was 35.1 ± 5.0 years (n = 2880) and for Panel B was 35.1 ± 5.0 years (n = 2204). The mean male age for Panel A was 37.4 ± 6.4 years (n = 1352) and Panel B was 37.9 ± 6.4 years (n = 1264).

The content of each panel was analysed. Panel A was composed of 99 autosomal recessive and three X-linked disorders, whereas Panel B had 282 and 25, respectively. Of particular note, some conditions included on both panels, such as ataxia–teleangiectasia, have also been associated with autosomal dominant conditions in the monoallelic state (*Chenevix-Trench, 2002*). No conditions were solely limited to autosomal dominant inheritance included on the panels. Overlap in the disease content on the two panels was then determined. On Panel A, 401 variants in 102 diseases were genotyped. On Panel B, 2717 variants in 307 diseases were genotyped. A total of 311 disorders covering 2746 mutations were genotyped across the two ECS panels. Of the 311 disorders, 98 were included in both panels. Panel A included an additional four disorders not covered by Panel B, whereas Panel B included an additional 209 disorders not found on Panel A (FIGURE 1A). Of the 2746 mutations, both panels screened for 372 mutations in 98 diseases (group 1) (FIGURE 1B). Unique mutations for the 98 shared diseases (group 2) included 20 on Panel A and 874 on Panel B. Mutations screened for unique diseases (group 3) included nine variants found in four diseases on Panel A and 1471 variants found in 209 diseases on Panel B. Therefore, of the 2746 mutations included on either panel, only 372 (13.5%) mutations in 98 disorders are shared between the panels. Panel A alone screens for 29 (1.1%) variants and Panel B alone screens for the remaining 2345 (85.4%) mutations.

The individual carrier rate was calculated for each ECS panel in its entirety. Panel A identified 1243 carriers (29.4%) whereas Panel B identified 1503 carriers (43.3%) (FIGURE 2), a statistically significant difference ($P < 2.2 \times 10^{-16}$). Carrier rates for each panel were calculated and compared for each mutation group. For group 1, Panel A identified 1141 carriers (27.0%) and Panel B identified 868 carriers (25.0%), which was not a statistically significant difference (FIGURE 2). In group 2, Panel A identified 17 carriers (0.40%) whereas Panel B identified 458 carriers (13.2%), a statistically significant difference ($P < 2.2 \times 10^{-16}$). Within group 3, Panel A identified 122 carriers (2.9%) and Panel B identified 469 carriers (13.5%), representing a statistically significant difference ($P < 2.2 \times 10^{-16}$).

The top 10 disorders identified for each panel were compared, revealing some variability in rank (TABLE 1). None of the disorders that were only included on one of the panels ranked in the top 10. The overall carrier rates for five of the top 10 disorders were statistically different ($P < 2.2 \times 10^{-16}$ to 0.0056). For mutations included in both panels (group 1), the carrier rates differed significantly between panel A and panel B for four of the disorders found to be in the top 10 for either panel (P = 0.0056 to 0.042) In all but three of the disorders investigated, the difference in carrier rates for only those unique mutations (group 2) was statistically different (TABLE 1), suggesting that the addition of mutations to Panel B explains most of the differences observed ($P < 2.2 \times 10^{-16}$ to 0.016).

As carrier frequencies for each mutation often vary based on ethnicity, a comparison of carrier rates of each panel was completed based on self-reported ethnicity. A total of 11 ethnicities were compared between the two panels

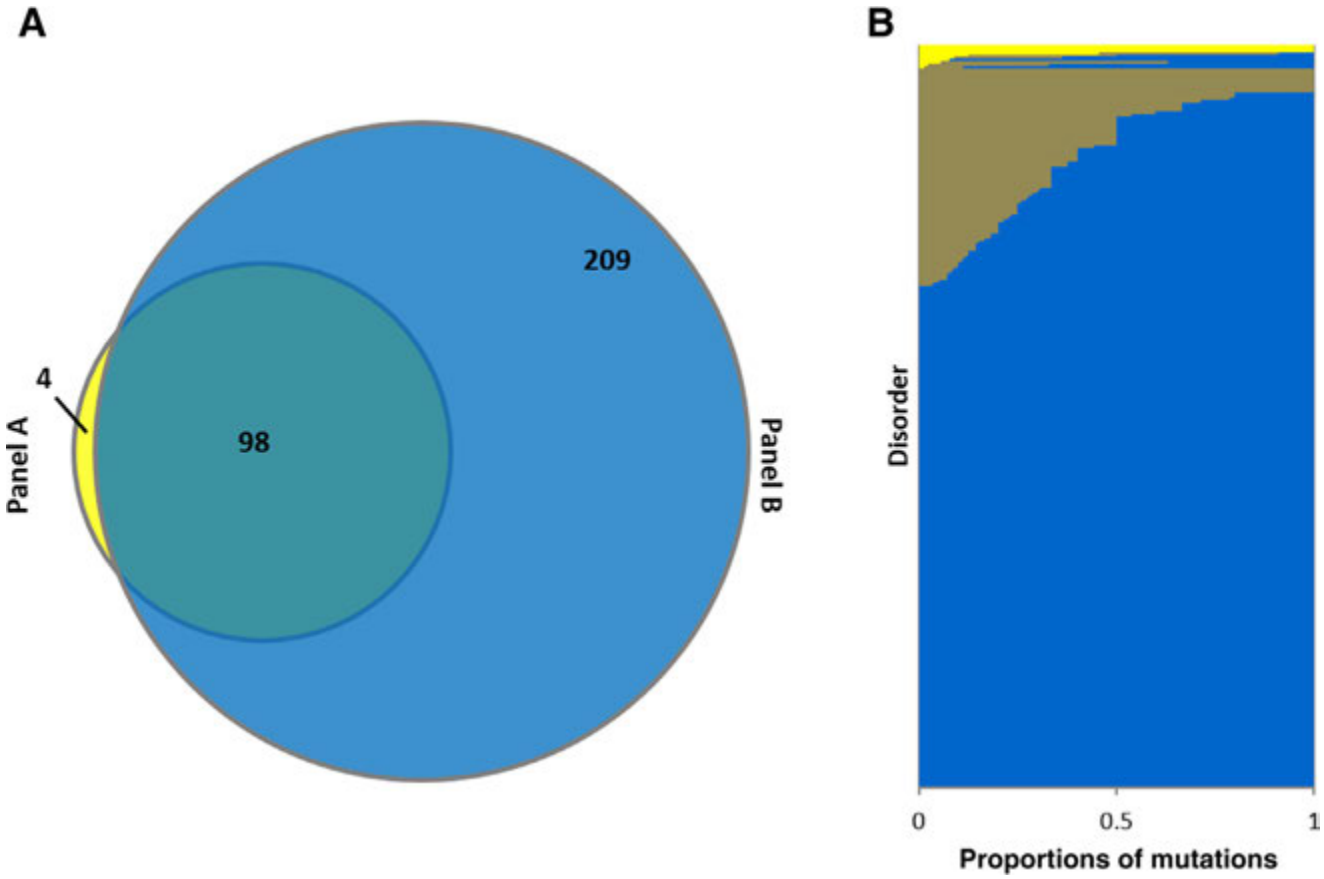

FIGURE 1 Comparison of expanded carrier screening (ECS) panel content. (A) The shared and unique disorders screened on each ECS panel; (B) stacked bar chart depicting the proportion of mutations shared or unique to each panel. Yellow, Panel A only mutations; olive green, shared mutations; blue, a B only mutations.

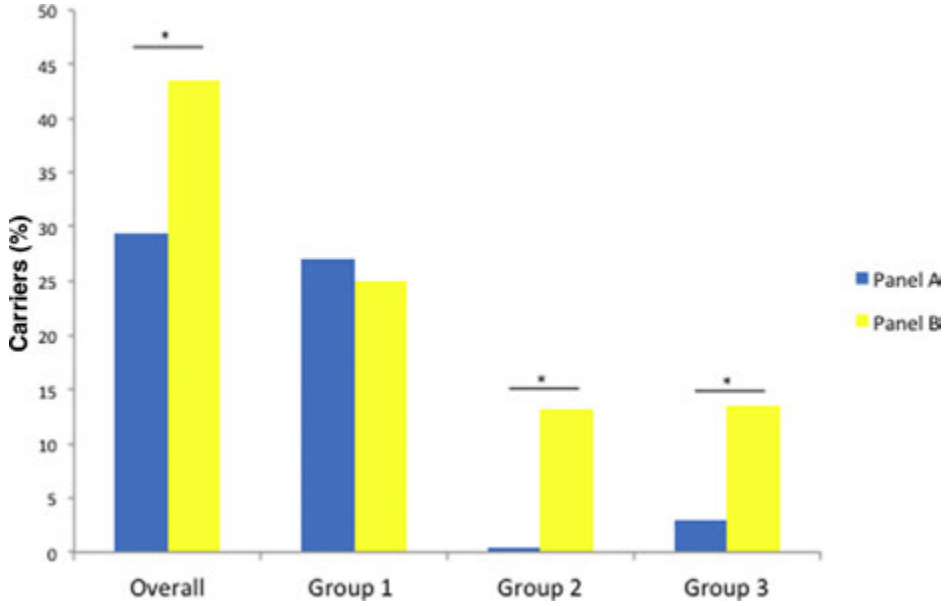

FIGURE 2 Carrier rates based on similarities and differences between Panel A and Panel B. For each mutation, it was determined whether it was shared (group 1) or was included in only one of the panels. For those mutations that were included in only one panel, it was further determined if the mutation was associated with a disorder screened by both panels (group 2) or by only one of the panels (group 3). The individual carrier rate was determined for these three categories. The differences in carrier rate for the two categories of mutations that were unique to each panel were statistically significant, *$P \leq 0.05$.

TABLE 1 COMPARISON OF CARRIER FREQUENCIES FOR TOP 10 DISORDERS OBSERVED ON EACH PANEL

Disorder	Panel A		Panel B		P-value		
	Rank	Carriers	Rank	Carriers	Overall	Group 1[a]	Group 2[b]
Cystic fibrosis	1	132	3	114	NS	NS	0.014
Pseudocholinesterase deficiency	2	103	5	99	NS	NA	NA
Spinal muscular atrophy	3	84	13	41	0.0056	0.0056	1
Non-syndromic hearing loss and deafness: related to GJB2	4	74	2	135	8.4×10^{-9}	NS	$<2.2 \times 10^{-16}$
Fragile X syndrome	5	72	6	63	NS	NA	NA
HbS sickle cell anaemia	6	67	10	49	NS	NA	NA
Alpha-1 antitrypsin deficiency	7	64	11	46	NS	0.028	3.1×10^{-5}
Gaucher disease	8	60	12	44	NS	NS	0.016
Familial Mediterranean fever	9	59	4	104	1.1×10^{-6}	NS	$<2.2 \times 10^{-16}$
Smith–Lemli–Opitz syndrome	10	54	7	55	NS	NS	NS
Biotinidase deficiency	34	7	1	216	$<2.2 \times 10^{-16}$	0.019	$<2.2 \times 10^{-16}$
Beta thalassemia	14	47	8	54	0.087	NS	NS
Phenylalanine hydroxylase	16	34	9	53	0.0028	0.042	2.3×10^{-8}

[a] Mutations included in both panels

[b] Additional mutations for shared disorders included on only one panel.NA, not applicable; NS, non-significant.

(TABLE 2). Of those, all but two (Middle Eastern and Mediterranean) had overall carrier frequencies that were significantly different ($P = 1.0 \times 10^{-10}$ to 0.031). Comparing the carrier frequencies across ethnicities for group 1 mutations revealed a significant difference only where ethnicity was unknown or not reported ($P = 0.020$). All but one ethnic subpopulation (Middle Eastern) had significantly different carrier frequencies when comparing group 2 mutations ($P < 2.2 \times 10^{-16}$ to 0.00064). Finally, all but two ethnicities (South Asian and Middle Eastern) had carrier frequencies that differed significantly between the two panels when comparing mutations in group 3 ($P < 2.2 \times 10^{-16}$ to 0.0010).

Panel A screened a total of 1206 couples, 15 (1.2%) of which were both partners were found to be carriers for the same disorder ('carrier couples'). Panel B screened 1186 couples, of which 37 (3.1%) were carrier couples. The proportion of carrier couples identified by each panel was significantly different ($P = 0.0017$). For each carrier couple, it was determined whether both or only one of the ECS panels would have identified them. Of the 15 carrier couples on Panel A, 14 of the couples would have been identified by both ECS vendors; the last couple was identified as a carrier couple for group 3 mutations (Supplementary TABLE 1). Of the 37 carrier couples identified on Panel B, 19 (51.4%) would have been identified by Panel A. The remaining 18 couples identified on Panel B would not have been found by the other panel for a number of reasons: in one case, the couple was a carrier for group 3 mutations; in four cases, only one of the partners would have been found to be a carrier by Panel A whereas the other would have been missed; in 13 cases, both partners would have been missed by Panel A because the couples were both carriers for group 2 mutations (Supplementary TABLE 1).

DISCUSSION

As use of ECS has become more prevalent, the number of genetic testing companies offering such screening keeps rising. Limited guidance from professional societies, however, has resulted in a wide variability in which disorders and associated pathogenic mutations are included in a screen (*Chokoshvili et al., 2017; Stevens et al., 2017*) This leaves physicians with an often confusing decision as to which ECS panel is best suited for their patient population. In this study, we compare and contrast two commercially available panels in a study population presenting to a fertility centre. Although 98 disorders were shared by both panels, only a limited number of mutations was common to both panels (FIGURE 1). To the best of our knowledge, this is the first study to investigate the similarities and differences between two commercially available ECS panels in the context of the effect on carrier and carrier couple identification rates.

Both of the commercially available panels studied here included only autosomal recessive and X-linked disorders. Indeed, these findings follow recommendations from the American College of Obstetricians and Gynecologists that highlight that expanded carrier screening panels should not include conditions with adult onset, such as hereditary cancer predispositions (*Rink et al., 2017*). These conditions are typically inherited in an autosomal dominant manner. Furthermore, population-based screening for these conditions is not currently practiced; however, expanded carrier screening panels are designed with this delivery model in mind.

It can be hypothesized that including additional mutations and disorders in an ECS panel will result in identifying additional carriers. Indeed, we find that the larger panel (Panel B) identifies a significantly higher proportion of carriers compared with the smaller Panel A (43.3% versus 29.4%) (FIGURE 2). Additionally, Panel B identifies carrier couples at a higher rate (3.1% versus 1.2%). Panel B is larger in two aspects: first, for those disorders screened by both panels, Panel B includes many more associated mutations; second, Panel B includes additional disorders that Panel A does not. The combination of these two differences results in the observed significant differences. What is the contribution of each of these factors? When looking at the overall population,

TABLE 2 COMPARISON OF CARRIER FREQUENCIES FOR INDIVIDUALS BASED ON SELF-REPORTED ETHNICITY OBSERVED ON EACH PANEL

Self-reported ethnicity (n)		Overall			Group 1[a]			Group 2[b]			Group 3[c]		
Panel A	Panel B	Panel A	Panel B	P-value	Panel A	Panel B	P-value	Panel A	Panel B	Panel C	Panel A	Panel B	P-value
Hispanic (480)	Latin American (328)	97	113	5.8×10^{-6}	93	50	NS	3	42	2.5×10^{-14}	1	37	2.2×10^{-14}
African/African American (377)	African (254)	80	73	0.031	79	56	NS	0	8	0.00064	1	11	0.00030
South Asian (277)	South Asian (127)	44	32	0.026	28	14	NS	2	11	9.0×10^{-5}	16	11	NS
East Asian (206)	East Asian (141)	13	40	2.0×10^{-8}	13	11	NS	0	25	4.2×10^{-11}	0	7	0.0017
Middle Eastern (75)	Middle Eastern (21)	23	7	NS	21	4	NS	0	1	NS	2	2	NS
Southeast Asian (71)	Southeast Asian (91)	11	37	0.00050	10	10	NS	0	18	1.6×10^{-5}	1	15	0.0010
Southern European (510)	Mediterranean (84)	160	31	NS	144	18	NS	3	8	1.4×10^{-5}	18	13	5.1×10^{-6}
Northern European (393)	European (805)	116	396	1.0×10^{-10}	108	233	NS	2	120	$<2.2 \times 10^{-16}$	10	133	2.5×10^{-12}
Mixed/other Caucasian (1089)	European and another selected ethnicity (158)	361	70	0.012	340	39	NS	5	16	2.5×10^{-11}	28	28	$<2.2 \times 10^{-16}$
Unknown/not reported (383)	Unknown/not reported (625)	132	270	0.0066	123	159	0.020	2	77	1.2×10^{-14}	8	78	1.1×10^{-8}
Ashkenazi Jewish (359)	Jewish or European and Jewish (381)	197	245	0.0024	178	175	NS	0	63	$<2.2 \times 10^{-16}$	33	84	7.6×10^{-7}

[a] Mutations included in both panels.

[b] Additional mutations for shared disorders included on only one panel.

[c] Mutations associated with disorders only screened on one panel.NS, non-significant.

both the addition of mutations for shared disorders (group 2) and the addition of more disorders (group 3) results in a significantly different carrier rate (FIGURE 2). These findings are not necessarily surprising, but reveal that when comparing ECS panels to each other, it is important to understand exactly how each panel is different (and similar).

An additional factor in choosing an ECS panel is the patient population that presents to the physician's practice. It is well-established that wide genetic variability exists both between individuals from different continents, but also variability within smaller communities (*The 1000 Genomes Project Consortium, 2015*). When we compare the carrier frequencies based on ethnicity for group 1 mutations, we find no significant differences (except for Unknown or Unreported). We find some interesting trends, however, when investigating what factors influence the differences (or lack thereof) in carrier frequencies for each ethnicity by each panel. For example, the carrier frequency in the Middle Eastern population does not change regardless of whether additional mutations are included in a panel, suggesting that either there is a lower incidence of disease in this population or that neither of the panels in this study includes mutations that are relevant to this population. We also identified one ethnicity (South Asian) where only one of the two unique mutation categories (groups 2 and 3) resulted in significant differences. These findings suggest that the addition of mutations may not always benefit every patient, but would allow for more universal coverage across different ethnicities, making expanded carrier screening an appropriate option for patients of all ancestral backgrounds. Thus, as a physician choosing the panel appropriate for her or his practice, it is important to understand how and whether the addition of mutations will benefit her or his specific patient population.

The clinical significance of ECS is identifying those couples or individuals that are at an increased risk of passing on a genetic disorder to their children. Here we show that Panel B identifies more carrier couples of autosomal recessive disorders and more carrier females for X-linked disorders. However, when comparing only those who were carriers for group 1 mutations, the differences are eliminated. In some cases, however, carrier couples and females from Panel B group 2 or group 3 mutations were carriers for mutations with mild phenotypes. In these cases, the effect on quality of life is minimal. For example, Panel B identified five carrier couples for biotinidase deficiency in which both partners carried the p.D444H mutation. Individuals homozygous for this mutation present with the more mild form of biotinidase

deficiency (partial biotinidase deficiency) and are easily treated with a daily vitamin (*Swango et al., 1998*). Individuals carrying this mutation in addition to a second, more severe mutation, may present with more severe symptoms, but again can be treated with daily vitamins. In addition, screening for biotinidase deficiency is now included in newborn screening guidelines; so even if a carrier couple is not identified, early intervention is possible for affected babies. Another example of Panel B identifying carrier couples for mild mutations is non-syndromic hearing loss (p.V37I) related to *GJB2*. Individuals homozygous for this mutation often present with more mild hearing loss symptoms that often manifest later in life (*Shen et al., 2017*). In cases in which the disease phenotype is mild or easily treatable or managed, the carrier couples may not choose to pursue preimplantation genetic testing in order to reduce the risk of having an affected child. Further study into the exact differences in disease content between the two panels is necessary to ascertain what clinical benefits arise from the inclusion of additional disorders or mutations, particularly when they are of a mild nature.

One significant limitation encountered during the study was how to compare ethnicities between the two panels. Because the choices available for selecting an ethnicity for each panel were different, we had to match them to the best of our ability. It is possible that the manner in which the categories were matched across the panels is not concordant with how a patient may select their ethnicity. Future studies with standard reporting for ethnicities are warranted to further investigate the differences in identifying carriers based on self-reported ancestry. Another limitation of the study is the inability to compare the criteria used to include mutations on each panel by each laboratory. All laboratories cite professional guidelines as criteria for the disorders and mutations included in their ECS panels; however, additional publications have revealed the wide variability of disorders and mutations included on a variety of panels (*Terhaar et al., 2018*). This reinforces our belief that clinicians should consider all options in the context of their specific patient population.

Like many other scientific advances and clinical applications, scientific and technological breakthroughs continue to improve diagnostic tools, further improving patient care. The panels included in the current study are based on screening for mutations using DNA microarrays, which require establishing which mutations should be included in the screen before producing the microarrays. New advances in genomic technologies, however, have begun to shift the testing platforms on which ECS, and other genetic tests, are based. Next generation sequencing (NGS) can scan the genome without any bias and identify variants, which can then be analysed using bioinformatics to assess potential pathogenicity (*Azimi et al., 2016*). The shift from microarray to NGS has already begun and will likely fully transition within the next 5 years. Currently, it is not recommended to report variants of unknown significance for carrier screening (*Vears et al., 2017*). Our data support a movement towards gene sequencing, which would allow for identification of more carrier couples through a methodology that detects additional mutations.

In conclusion, as panels expand to screen more and more disorders, several of the already established recommendations become even more important to which healthcare providers should adhere. These recommendations include offering both pre- and post-test genetic counselling to the patients so that they are informed of the available screening options along with the benefits and downsides to each and reporting carrier status for mutations that are known to have a well-defined phenotype. With advances in assisted reproductive technologies such as preimplantation genetic testing for monogenetic disease, it has become routine in fertility centres to perform carrier screening on patients to facilitate the likelihood of successful pregnancies and healthy children. The effectiveness of achieving these goals, however, is dependent on the ability to identify carriers and carrier couples with these known mutations. The increased detection of these carriers and carrier couples is bound to expand the reproductive healthcare options, including preimplantation genetic testing for single gene disorders, to reduce the risk of having unaffected biological children or planning for interventional treatments for affected children that will improve their quality of life.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.rbmo.2018.11.018.

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Received 29 March 2018; received in revised form 2 November 2018; accepted 8 November 2018.