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Expanded carrier screening: A review of early implementation and literature

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ABSTRACT

Carrier screening is the practice of testing individuals to identify those at increased risks of having children affected by genetic diseases. Professional guidelines on carrier screening have been available for more than 15 years, and have historically targeted specific diseases that occur at increased frequencies in defined ethnic populations. Enabled by rapidly evolving technology, expanded carrier screening aims to identify carriers for a broader array of diseases and may be applied universally (equally across all ethnic groups). This new approach deviates from the well-established criteria for screening models. In this review, we summarize the rationale for expanded carrier screening using available literature regarding clinical and technical data, as well as provider perspectives. We also discuss important avenues for further research in this burgeoning field.

Introduction

Rapid changes in genomic analytic technologies now enable new implementations of carrier screening, the practice of screening individuals or couples in order to identify those with the highest odds of conceiving children affected by genetic disease. Like the traditional carrier screening practice discussed by Wick and Rose in this journal issue, the newer approach also targets autosomal or X-linked recessive diseases that primarily affect newborns and children by causing cognitive and physical disability and/or shortened life span. Both approaches share the same objective—to inform couples of their risks so that they may consider reproductive options.

Where the approaches differ are in the number and types (including inheritance, severity, and treatability) of diseases screened and the individuals to whom they are offered. Carrier screening has historically assessed a relatively small number of diseases selected based on similar characteristics—high frequency in a certain subpopulation and association with severe morbidity or mortality. Now, "expanded carrier screening" (ECS) is the practice of screening all individuals for dozens to hundreds of diseases, some with lower frequencies or severity grades, typically without tailoring to a person's reported ethnicity.

Widespread ECS is achievable only because new technologies have dramatically increased the amount of genomic area that can be analyzed at a reasonable cost. These same advances have enabled other genomic tests, such as whole-exome- and whole-genome sequencing, that may be used in a diagnostic setting. In contrast to those, ECS is targeted at diseases already described in the medical literature and recognized by medical geneticists. As such, ECS represents the recognition of the newfound practicality of screening a large number of known diseases, rather than a protocol for discovery of novel diseases or genotype–phenotype correlations.

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In this article, we describe the rationale for expanded carrier screening as well as its current landscape, including professional organization statements, provider perspectives, published laboratory and clinical data, and counseling considerations. Given its relative infancy, significant contributions to the medical literature on ECS will continue to accrue rapidly. Consequently, we conclude the article by highlighting the most prominent knowledge gaps, and suggest directions for future work.

Rationale for ECS

As described above, ECS encompasses two components that are departures from long-standing screening protocols: a larger list of diseases coupled to pan-ethnic application. In the context of decreasing costs for genomic analysis, we will expand on each of these components.

The reasons for ethnicity-driven screening protocols in the United States (US) are described in the previous article by Wick and Rose. However, pan-ethnic or universal screening for two diseases, cystic fibrosis and spinal muscular atrophy, has been recommended by the American College of Obstetricians and Gynecologists[1] (ACOG) and/or the American College of Medical Genetics and Genomics[2,3] (ACMG). In the case of spinal muscular atrophy, ACMG considered the relatively high prevalence in all ethnic groups (though there has since been data that establishes some inter-ethnic variability, ACMG nonetheless reaffirmed its position in 2013). In contrast, cystic fibrosis demonstrates wide ethnic disparity in its prevalence. Screening guidelines for cystic fibrosis originally targeted Caucasians and Ashkenazi Jewish (AJ)[4] populations. However, in 2005 ACOG updated its recommendation to justify pan-ethnic screening as "it is becoming increasingly difficult to assign a single ethnicity to individuals."[1] Ross[5] extended this reasoning to hemoglobinopathies and other diseases screened in targeted populations, calling for equitable access to reproductive information.

Recent demographic changes in the US have created challenges to reliable ethnic identification, consequently leading to increased likelihood of disease occurrence in non-targeted groups. For example, up to 12% of infants diagnosed with a beta-hemoglobinopathy via newborn blood-spot analysis in California during the early 1990s were outside of the groups included in ACOG's carrier screening guideline.[6] Such demographic changes are sure to continue, indicating that pan-ethnic carrier screening will improve detection of at-risk couples. The 2010 Census shows substantial increases in individuals reporting mixed racial ancestry, especially among those of reproductive age and younger.[7] Similarly, the Jewish intermarriage rate is currently 48%,[8] assuring that diseases currently screened in the AJ population will persist in other groups, as has occurred with Tay–Sachs disease.[9] The shift to pan-ethnic offering of any disorder screened can be summarized most simply as an equitable, effective model for an evolving population.

In addition to removing ethnicity considerations, the ECS model also proposes expanding the list of diseases identified in routine carrier screening. Current guidelines stipulate screening only for cystic fibrosis, spinal muscular atrophy, and/or hemoglobinopathies in the largest U.S. subpopulations.[1,3,10] Tay-Sachs disease screening is offered to individuals of Cajun or French Canadian ancestry.[11] Individuals of AJ ancestry may be offered screening for an additional three or eight diseases, depending on the professional guideline that is followed.[11,12] While screening guidelines already enumerate more diseases in AJ individuals than in any other population, addition of even more diseases has occurred. Scott et al.,[13] assessed acceptability, uptake and results of screening for 16 disorders in the New York-based AJ population, finding it to be feasible and acceptable. An at-home testing model for 19 diseases in the AJ population is being evaluated on an ongoing basis,[14] and a comparison of six laboratories found "AJ panels" of up to 25 diseases.[15] While screening criteria have typically focused on the most severe diseases with carrier frequencies exceeding 1%, these panels depart from strict adherence by including diseases that have variable or milder expressivity (e.g., Gaucher disease), or lower carrier frequencies (e.g., *NEB*-related nemaline myopathy). ECS is well underway in the AJ population.

Considering an expanded disease list in all populations is reasonable when noting that Mendelian diseases account for 20% of infant mortality and 18% of infant hospitalizations in the US.[16]

Many public health and individual benefits of ECS were proposed by Kingsmore, including greater availability and utilization of treatments and preventions, diagnostic cost and time reduction, quality of life improvement, and decrease of unnecessary treatments, among others.[16] There are few "common" inherited diseases (of a frequency comparable to sickle cell disease, alpha-thalassemia, and cystic fibrosis), but the collective incidence of "rare" diseases surpasses the incidence of those common ones.[17] Since population screening has consistently resulted in reduced incidence of the diseases of interest,[18,19] it is reasonable to assume that large-scale ECS implementation would likewise impact a larger portion of related mortality and morbidity.

The increasing number of expanded carrier screens performed in recent years has enabled more objective estimations of carrier frequencies and associated risk, including those of rare diseases. For instance, data from a large multiethnic population showed that the risk of a collective group of 89 diseases exceeded that of open neural tube defects or trisomy 21 pregnancy for a 20-year-old woman.[20] Since the prevalence of trisomy 21 and open neural tube defects has been used to justify universal screening for these disorders,[21,22] and since recessive disease prevalence is likewise typically cited as an important criterion for screening,[12] similar data for rare disease raise consideration for population-based implementation.

Beyond reproductive decision-making, an expanded disease panel may also widen the scope of objectives that can be achieved through carrier screening. There has been reliance on newborn screening to detect recessive diseases postnatally where early interventions result in improved outcomes. Prenatal awareness of substantial risk may confer even greater benefits, since certain diseases (e.g., medium chain acyl-CoA dehydrogenase deficiency) may cause long-term sequelae even before newborn screening results are available, or may be diagnosed at ages by which another affected

Box–Principles of pre-test.

Carrier screening identifies couples who may conceive an at-risk pregnancy/birth.There are three overarching groups of anomalies: inherited genetic diseases (e.g., cystic fibrosis), sporadic genetic diseases (e.g., Down syndrome), and diseases without obvious cause (e.g., spina bifida). Carrier screening addresses the first group.

Family history does not usually indicate risk for these diseases.

The diseases tested range in their presentations: cognitive disability, physical impairment, shortened lifespan, or some combination of these.

In most cases, both partners must be carriers for the same disease in order to have an increased risk of an affected offspring. While it is common to be identified as a carrier for one disease, it is uncommon for both partners to carry the same disease. If found to be a carrier, the usual next step is to test the partner for the same disease.

When both partners are carriers of the same disease, next steps to consider are prenatal diagnosis via amniocentesis or chorionic villus sampling, or preconception options, such as preimplantation genetic diagnosis, gamete donors, or adoption.

Typically, individuals do not experience any symptoms of the diseases they carry. However, it is possible for carrier screening to reveal personal health effects. Once testing is completed, if applicable, specific disease details and all implications will be discussed. Genetic counseling should be made available.

No testing addresses all possible birth defects and diseases. Carrier screening, and other available tests and ultrasounds, identify many of the most common conditions.

Adapted from Edwards et al.,[27] Grody et al.,[26] and Elias and Annas.[43]

pregnancy could have already occurred.[23,24] Furthermore, carrier status of certain diseases may also raise awareness of maternal obstetric complications and affect management.[25]

In summary, carrier screening can be expanded in multiple ways with benefits to each: more individuals, resulting in equitable application of genomic technology; more diseases to better address the spectrum of genetic disease; and more objectives, i.e., to not only avert affected births, but also to improve neonatal/pediatric treatments and reduce maternal morbidity.

Professional society statements on expanded carrier screening

The ACMG issued the first position statement on ECS, which primarily addressed criteria for disease inclusion on an ECS panel.[26] Among these were the recommendations that phenotypes should warrant consideration of prenatal diagnosis, and that the genes and specific mutations associated with the diseases should be well understood in order to assess risk. Where diseases vary in severity or presentation (including those with onset in adulthood), patients should be made aware of and consented to be screened for such. It also briefly addresses pre- and post-test education and counseling considerations, including the need for a generic rather than disease specific consent approach and indications for formal genetic counseling.

This year, a comprehensive "Points to Consider" document was jointly issued by the ACOG, ACMG, Society for Maternal-Fetal Medicine, National Society of Genetic Counselors, and Perinatal Quality Foundation.[27] It also addresses the phenotypic and molecular characteristics of diseases to be tested, and further expands on pre-test consent and post-test management. Based on these statements, and on generic informed consent model put forth by Elias and Annas[28]; Box describes an example of pre-test discussion. A recent survey found most individuals preferred more detailed, rather than briefer, generic consent models, and a sizable minority indicated the opposite.[29] More thorough study of patients' pre-test needs is warranted, since this study's conclusions may not be generalizable.

Post-test, formal genetic counseling is indicated when an at-risk couple (having a 25% chance of an affected child) is identified. In other cases, post-test education and counseling centers on carriers and includes a discussion of residual risks and alternative testing options for the partner, including sequence analysis or enzymatic studies.

Lastly, in recognition of ECS adoption outside the US, the European Society of Human Genetics will also be issuing guidelines for responsible implementation. In addition to reviewing ECS in the context of carrier screening that has been performed to varying degrees in Europe, the draft also covers clinical and counseling considerations, and cautions about diseases or mutations that have milder expressivity and do not affect reproductive decision making.[30]

None of these publications indicate preference for ECS over traditional screening protocols, but do acknowledge its benefits, increasing utilization, and put forth justifiable ways for it to be implemented, at the discretion of the individual physician.

Testing experience

Analytical performance

Overall, two primary approaches to expanded carrier screening exist: targeted analysis of pre-selected mutations known to have valid associations with a particular disease (i.e., targeted genotyping) or sequence analysis via next-generation methodologies. The latter method detects a broader

array of variants, which may have similar, weaker, unknown, or no pathogenic effects.

Though sequence analysis is becoming more prominently available, most U.S.-based commercial laboratories currently use the former approach. Results from a published validation study comparing a microarray-based platform assessing 454 variants causing 105 diseases to single-gene based methods, found similar analytical performance.[17] This method was further found to have 100% concordance with a clinical population of known carriers.[31]

Next-generation sequencing (NGS) promises high clinical sensitivity in assayed genes, though issues of variant interpretation are considerable. Bell et al.,[32] found high analytic sensitivity and specificity using an NGS approach for 448 recessive diseases.

Clinical experience

The only clinical data on ECS published to date compiled results from targeted-genotyping based screening of a multiethnic U.S. population of 23,453 individuals. Approximately one in four individuals carried at least one disease and 69–77% of these carriers were not included in guidelines issued by ACMG or ACOG. In addition, carriers of diseases traditionally screened in certain ethnic subpopulations were found to be present in individuals of other ethnicities.[33] Ethnic-specific carrier frequencies were reported for the first time for many diseases.

NGS data has been published recently after carrier assessment for a small number of genes. Greater numbers of carriers per gene were identified, as expected. In 11,691 individuals screened by NGS for 15 genes, approximately one-quarter carried mutations not typically included in targeted panels.[34] When assaying *CFTR* mutations by NGS, Lim et al.[35] concluded that current genotyping panels underperform in minority populations, particularly South and East Asians. Cystic fibrosis is already recommended to be screened pan-ethnically, yet the mutations most commonly assayed were determined because of their prevalence in the Caucasian population. A population-based screening program ideally serves all subgroups well. Thus, equitable application of ECS may actually necessitate an NGS approach, at least for a subset of genes.

Diseases screened

Professional society statements do not specify diseases that should be included or excluded in an expanded carrier screening panel.[26,27] This has led to variability in current commercially available screening panels, which may lead to inefficiencies or confusion among providers and patients. A committee issuing guidelines from the European Society of Human Genetics analyzed the diseases tested by four laboratories, ranging from 74 to 210 diseases, and found that only 29 were in common.[28] Within these diseases, differences in methods and mutations assayed also contribute to the current lack of uniformity in offering expanded screening.

Existing professional statements stipulate that diseases warrant inclusion particularly when they exhibit cognitive disability or adverse impact on quality of life. Diseases that would be tested by, and especially alter management based on results of, prenatal diagnostic methods fit these criteria. While no organization suggests that any specific diseases be definitively excluded from a panel, they do suggest that those with mild phenotypes, adult-onset presentation or low penetrance be made optional.

At the heart of these criteria are measures of severity, though this is easily subject to individual discretion. To address the pitfalls of incorporating severity into development of broad screening programs, Lazarin et al.[36] developed a classification algorithm that assigns severity (profound—4, severe—3, moderate—2, and mild—1) based on discrete disease characteristics. Based on the ACMG's assessment of severity in diseases considered for newborn screening, this scale enables an objective assessment of an individual laboratory's screening panel, and a means to facilitate discussions of ECS panels with patients.

In contrast with the rationale for single disease guidelines, criteria such as carrier and disease frequency and clinical sensitivity of available testing are no longer stipulated in the expanded screening statements. They are mentioned only insomuch as to ensure that providers and laboratories are aware of the need to communicate *a priori* and residual risk data.

Severity is often determined by the deleterious effects of the mutations in a gene. The history of cystic fibrosis carrier screening and the broad phenotypes associated with this disorder have revealed the challenges of classifying these gene effects.[37] In particular, as NGS approaches become more common, variant interpretation in reproductive carrier screening will need as much attention and resource usage as in other areas of clinical genetics. Since personal decisions may result from carrier screening results, often without the ability to fully observe fetal effects, transparent methods of variant classification are of utmost importance.[38] Variants of uncertain significance add complexity to patient counseling. Currently most laboratories performing NGS for the dedicated purpose of carrier screening do not reveal these variants in result reports, as is recommended by the joint. Points to Consider statement.[27] However, this practice may not be uniform, and variants of uncertain significance may be revealed if ordering a gene sequence analysis that a laboratory designed for diagnostic, rather than screening, purposes. Therefore, providers ordering ECS using NGS methods should be cognizant of a laboratory's variant classification and reporting protocols.

Provider perspectives

Practices and attitudes amongst physicians, genetic counselors, and other providers are likely still evolving with ECS. To date, perspectives have been positive, though accompanied by some concerns regarding implementation. There is also a seeming dichotomy between screening preferences for oneself and for one's patients.

Ready et al.[39] surveyed obstetricians, reproductive endocrinologists, nurses, and other health care providers, assessing basic genetic and genetic screening knowledge. Respondents were generally accurate in their responses to questions about recessive inheritance, consistent with other similar data.[40] Regarding ECS specifically, 78% personally preferred being screened for more, rather than less, disorders. Personal interest was likewise high among genetic

counselors, of which 80% would personally elect ECS for themselves.[41]

Physicians and genetic counselors also express concern regarding practical implementation of ECS, including pre- and post-test education and counseling. ACOG Fellows surveyed expressed discomfort having both pre- and post-test discussions about ECS and over half stated that patients should receive pre-test counseling from a genetic counselor.[42] Nearly 40% of genetic counselors also believed that pre-test counseling should be administered by a GC, though other alternatives were acceptable to the remainder.[41] A focus group of genetic specialists agreed that counseling before and after testing was important, and also expected that reproductive health care providers would be generally comfortable with this, since there is similarity between ECS and screening for many disorders in the Ashkenazi Jewish population.[43]

These studies indicate general agreement regarding handling of ECS results—genetic counseling is indicated in cases of positive results (either one partner, or both partners for the same condition), but negative results do not typically necessitate formal counseling. Of note, several laboratories that perform ECS also provide post-test genetic counseling services, typically by telephone.

While the provider surveys to date have indicated general acceptance and strong personal interest for ECS, actual utilization lags significantly. Only 15% of ACOG Fellows offered ECS to all of their patients and 77% indicated that ECS should only be offered based on family history, race/ethnicity, or as recommended by ACOG.[42] This pattern was also found among genetic counselors, in which 80% would personally elect ECS for themselves, yet very few were offering it to all of their patients.[41] The discrepancies observed here merit further investigation, and may originate from the practical implications of the counseling perspectives discussed above.

Conclusion

Expanded carrier screening is a new approach, with much to be settled including diseases that should be tested, optimal pre- and post-test counseling, and impact on clinical and public health outcomes. Nonetheless, it is becoming more common.

We estimate that over 200,000 individuals have undergone ECS in 2015. This is a small percentage of the four million annual pregnancies in the US, but is more considerable in the context of the population that currently has carrier screening of any kind.

Current literature and personal observation point to the need for research on the following specific topics:

1. Cost-effectiveness in comparison to traditional carrier screening and no carrier screening at all, for public health effect consideration.
2. Patient and provider perspectives on diseases to be included or excluded, or other means of establishing greater uniformity among different laboratory panels.
3. Accurate carrier frequencies and test sensitivity data for each disease being screened, in addition to more robust variant classifications.
4. Methods of pre- and post-test counseling that balance the increased load of genetic information with already strained genetics specialist resources.
5. Education models for increasing awareness and understanding among non-genetics providers and the general public.
6. Clinical outcomes among at-risk couples.
7. Patient satisfaction and experience before, during, and after undergoing ECS, in comparison to traditional carrier screening and no carrier screening at all.

While further data on these topics are developed, ECS continues to be offered and performed in the US. Outside the US, whether and how to integrate ECS into their health care systems is a new topic, which may raise similar and unique considerations as well.[30,44]

Here, an overview of ECS is presented. Examination of the criteria historically used to design screening programs reveals limitations due to increasing population diversity and little disease coverage in relation to total available opportunity. Initial laboratory data has established that testing is reliably accurate and reinforces the presumptions that many people carry diseases for which they are not being screened. Current provider perspectives generally accept the utility of ECS, while also revealing concerns about genetic counseling and the limitations of current genetics knowledge. Finally, many professional organizations have issued statements acknowledging the described benefits, while still withholding an opinion for ECS over traditional screening, due to the concerns described. Undoubtedly, this field will continue to evolve, with substantial new developments expected in coming years.

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