Clinical Utility and Practical Implications of Carrier Screening

GENETIC SCREENING AND COUNSELING is an important part of preconception and prenatal care.[1] The previous articles in this supplement reviewed current guidelines regarding genetic carrier screening, the limitations of these guideline-based recommendations, and the evolving science of expanded carrier screening. This article explores the practical implications of carrier screening, including cost, patient acceptance, social and ethical implications, and barriers to genetic screening implementation.

Accessibility

The Centers for Disease Control and Prevention set forth a framework called ACCE, which describes criteria that can be used to evaluate genetic screening tests.[2] These criteria include analytical validity, clinical validity, clinical utility, along with associated ethical, legal, and social implications. Economic costs and benefits associated with actions as a result of testing are among many questions to be considered.[3]

Insurance Coverage

Insurance providers offer varied coverage of carrier testing for genetic diseases according to guideline recommendations published by the American College of Obstetricians and Gynecologists (ACOG).[4] Carrier screening for cystic fibrosis and spinal muscular atrophy is covered for individuals seeking preconception or prenatal care.[5] However, for conditions other than cystic fibrosis and spinal muscular atrophy, carrier screening is not considered medically necessary unless there are positive implications of personal or family history, or the individual belongs to a high-risk ethnic group.[5,6,7] Insurance plans typically still regard expanded carrier screening as having unproven clinical utility or not being medically necessary.[6,7]

The molecular diagnostic reimbursement landscape is expected to change. One driver to this change is the rapidly declining cost of next-generation sequencing (NGS) used in expanded carrier screening.[8] In fact, it may be cheaper to use commercial expanded carrier screening panels instead of testing for individual genetic conditions.[9] Another factor is the effort to increase transparency in billing procedures. In the past, a genetic test may have been billed under a number of current procedural terminology (CPT) codes—a method known as code "stacking."[10] This lack of standardization leads to a wide variation in reimbursement amounts for the same genetic test submitted by different laboratories.[10] In addition, because the same set of CPT codes are used for genetic tests for a variety of conditions, payers do not know which diseases are being tested.[10] The American Medical Association recently approved a new single CPT code for expanded carrier screening.[11,12] This new CPT code is expected to take effect January 1, 2019,[13] and may improve the standardization of billing practices with greater transparency to payers.

Cost Effectiveness

The primary value of expanded carrier screening is to inform prospective reproductive partners about their risk of passing on serious genetic conditions to their offspring, and use this information to guide their plans for family building along with their personal values.[4] The majority of reproductive couples at risk for passing a serious disease to their offspring will alter their reproductive plans.[14] Affected births and their associated treatment costs can then be avoided.

The cost effectiveness of expanded carrier screening has been compared to guideline-based carrier screening.[15] Azimi et al compared the health and economic outcomes of expanded carrier screening using NGS technologies to either no screening, or conventional carrier screening for 14 diseases, recommended by professional societies.[15] Investigators used a decision tree analysis to capture patient ethnicity, carrier prevalence for each disorder, detection rates, healthcare processes (eg, treatments for recessive disorders), patient behaviors and decisions (eg,

TABLE 1. Cost Effectiveness of Expanded Carrier Screening, Compared With Conventional Carrier Screening of 14 Genetic Conditions Recommended by Professional Societies[15]

	Conventional Carrier Screening	Expanded Carrier Screening
Cost per life year gained	$33,812	$29,498
Cost for each affected birth avoided	$1.33 million	$1.14 million

Adapted from Azimi M, Schmaus K, Greger V, et al. Carrier screening by next-generation sequencing: health benefits and cost effectiveness. *Mol Genet Genomic Med.* 2016;4(3):292-302.

use of in vitro fertilization, pregnancy continuation), costs, and health utilities.[15] Performing a simulation of 1 million couples representative of the United States general population, investigators found that expanded carrier screening results were associated with lower costs for each affected birth avoided (**Table 1**).[15]

Another health economics study compared an expanded carrier screen of 176 conditions to minimal screening (cystic fibrosis and spinal muscular atrophy only) and no screening.[16] The authors estimated that each birth screened with expanded carrier screening would prevent about $3000 in lifetime medical costs, and this cost effectiveness is comparable to standard-of-care screening recommendations for inherited cancer risk.[16]

None of the existing cost effectiveness studies of expanded carrier screening have considered the expected increase in treatment costs for orphan diseases. In recent years, orphan drug approvals for fatal diseases, such as cystic fibrosis, have expanded treatment options for affected patients.[17] The average annual cost for orphan drugs are about 5 times higher than the cost of nonorphan medications.[17] In 2016, the annual cost per patient was estimated to be over $140,000 for an orphan drug, compared to less than $28,000 for a nonorphan medication.[17]

An increasing number of new and expensive orphan treatments continue to enter the market.[17] Increased availability of orphan drugs may increase the lifetime treatment costs of recessive genetic conditions, which may further increase the economic value of expanded carrier screening.

Another drawback of the available cost effectiveness studies is that the cost of follow-up counseling is not explicitly included in current models.[18] However, some expanded screening panel providers offer genetic counseling support as a key component of their services.[19,20] Payers should consider the overall costs when selecting expanded carrier screening service providers. This includes costs associated with follow-up and genetic counseling.

Patient Perspective

Genetic screening is voluntary.[21] Other factors beyond those related to costs and insurance coverage may affect the acceptance and uptake of expanded carrier screening. Data, however, is limited regarding patient interests and perceptions in expanded carrier screening.[22]

In a qualitative study among anonymous women in online chat rooms for pregnant women and women trying to conceive, test impact, measurable benefits, remedy and action were the predominant patient perceptions of a screening test's clinical utility.[23] Other factors influencing patient acceptance are the familiarity with the specific genetic diseases screened, availability of acceptable reproductive options, high perceived benefits, and low perceived social barriers (such as a low risk of stigmatization).[24] Furthermore, the ease of screening procedures has also been reported as a reason to accept screening.[24] Pretest information overload is perceived as undesirable, and women prefer to receive pretest information preconceptionally rather than during pregnancy, and in the form of a written leaflet prior to a visit with a provider.[25]

Ethical Concerns

Genetic reproductive screening raises potential ethical concerns. Fortunately, the best practices in implementation can mitigate many of these potential ethical issues. One area of concern is whether or not valid pretest consent can be obtained.[26] For expanded carrier screening panels, as the number of included diseases increases, obtaining valid informed consent prior to testing becomes more difficult because of "information overload."[26] A possible solution is to obtain generic consent where patients would be informed about the general types of possible test results and implications.[26] The American College of Medical Genetics and Genomics (ACMG) has acknowledged the necessity and importance of generic consent in expanded carrier screening.[27]

Another concern is false reassurance.[26] A negative screening result may provide false reassurance, as residual risks are present due to a test's incomplete sensitivity.[26] Patient misperception may also lead to the assumption that pregnancy risks other than those caused by recessive diseases will be avoided given a negative screening result.[26] In the case of an insufficiently validated screening panel, or patient misunderstanding, couples may make unwarranted reproductive decisions (eg, refraining from conceiving children) when such actions would not have been necessary.[26] Patient education before and after the genetic screening test can decrease occurrences of misunderstanding.

The discovery of one's own carrier status may have unexpected effects on psychological well-being, perceptions of health, and feelings of stigmatization.[26] Preconception screening tests can reduce emotional distress from positive results. There is less pressure on the parent to make immediate prenatal testing decisions with less time constraints and more reproductive options than screening during pregnancy.[26] Moreover, as genetic screening tests become more common, more people will understand that many individuals are carriers for a small number of genetic variants, and this knowledge may decrease anxiety.[26] Although members of particular subpopulations may feel stigmatized as a result of being a disease carrier, pan-ethnic whole-population screening may actually decrease stigma[26] and reduce ethnic-based biases.[22] In this respect, expanded carrier screening may reduce the risk of stigmatization of certain ethnic groups and increase equity.[26]

Expanded carrier screening enables early diagnosis and

treatment.[26] It is probable that couples planning pregnancies will consider preimplantation genetic diagnosis for treatable disorders.[26] Although preimplantation genetic diagnosis has focused mainly on decreasing the risk of passing on serious conditions, a shift toward the improvement of human traits is theoretically possible, and will have ethical implications.[28]

Ethical concerns of preconception or prenatal carrier screening and the resulting avoidance of the conception of affected offspring may impede the search for a cure for already affected patients, as the birth prevalence of affected children will decrease.[26]

Although many ethical concerns have been raised, most of them can be addressed by best practices in implementation.

Implementation Barriers and Current Best Practices

Expanded carrier screening is an evolving technology and has only recently become available. Implementation barriers include the lack of standardization among different laboratories, pre- and posttest follow-up management, and provider misperceptions.

Technical Barriers

Laboratories offering expanded carrier screening differ in the number of conditions tested, methodologies, and result interpretation. In a comparison of expanded screening panels among 4 laboratories, only 29 of up to 210 screened conditions were common among these laboratories.[22] Current laboratories screen for up to 549 diseases, and guidelines listing standardized diseases that should be included in expanded screening panels are not available.[26] Some expanded screening panels include diseases of mild or moderate impact, which may pose challenges in pretest counseling and consent.[22]

Different laboratories may use varying methodologies and approaches in result interpretation.[22] Although some laboratories test for a predefined list of common genetic variants, others test for any variants recognized in the literature as well as novel variants.[22] Testing only for a predefined list of variants reduces cost, turnaround time and variant interpretation challenges.[22] However, detection of a more comprehensive list of variants, including novel variants, will identify more at-risk couples.[22] An increased identification of carriers may create clinic workflow concerns.[22] Hence, a robust variant curation and classification system should be followed, so that only pathogenic variants are reported.[22]

In addition to the National Society of Genetic Counselors, the Perinatal Quality Foundation, and the Society for Maternal-Fetal Medicine, ACMG and ACOG, issued a joint statement regarding expanded carrier screening, including recommendations for conditions to be included in expanded carrier screening panels and variant interpretation.[29] However, this joint statement does not specifically recommend a list of conditions to be included or specific methodology for variant curation. Moreover, it is standard practice to not report variants of uncertain significance found by expanded carriers screening to patients.

Given the current lack of standardization of expanded carrier screening panels, some experts have recommended that clinicians and payers consider the "bottom line" measurement of a screening test's performance, which is the ability of a test to maximize the detection of couples at risk of having an offspring affected by a severe disease.[22] This concept of an "at-risk couple rate" in test performance, incorporates many important components. These consist of the severity of the diseases tested, mutation prevalence, and methodology used.[22]

Pre- and Posttest Management

In addition to technical laboratory challenges, there are also practical concerns with the increased frequency of identified carriers and the feasibility of adequate pretest education and posttest follow-up.[22] Traditionally, only a limited set of conditions and testing information are to be discussed with patients prior to a carrier screening test.[22] On the other hand, expanded carrier screening necessitates the use of a more generalized consent procedure.[22] In a survey of genetic counselors, although the majority (92%) state that all patients should receive pretest counseling prior to receiving expanded carrier screening, most (67%) agree that trained providers other than genetic counselors can conduct pretest counseling. Additionally, 31% support the use of written or media alternatives for pretest counseling.[21]

Posttest management is of particular concern if the disease is unfamiliar.[22] Genetic counseling and education should be offered for those individuals who receive positive results, but patients should also learn about residual risks when results are negative.[22]

Although screening male and female reproductive partners at the same time can shorten the screening process, this approach is costly.[22] When an individual is screened only after the discovery of the other partner's carrier status, the screening, results delivery, and education should be as expedient as possible.[22]

Based on the current availability of genetic counselors, personalized genetic counseling to accompany every positive result may not be realistic.[22] Potential solutions include telephonic or online genetic counseling,[22] or a combination of automated notifications, web education, and genetic counseling.[30]

Provider Misperceptions

In a survey study of women's healthcare providers, 40.1% of respondents reported concerns that genetic test results may not remain confidential, and 37% were worried that

positive genetic screening results may increase a patient's insurance rates.[31] Importantly, the Genetic Information Nondiscrimination Act and the Health Insurance Portability and Accountability Act offer patient protections by prohibiting health insurers from setting premiums or determining eligibility based on genetic information.[31,32] Continuing education is needed to address provider misperceptions regarding insurance discrimination and confidentiality of test results.[31]

Taken together, although expanded carrier screening is an evolving new technology, current literature provides insights regarding potential best practices for panel selection, as well as patient pre- and posttest education and counseling.[22] Research and further developments on optimizing screening panels, pre- and posttest counseling and education are expected. [22] Meanwhile, patient decision making and preferences, clinical outcomes, and optimal and efficient counseling methods are areas for further research.[22] Provider education can address misperceptions regarding test result confidentiality and insurance discrimination.[31]

The Role of Expanded Carrier Screening in Preconception and Prenatal Care

Preconception carrier screening increases a couple's reproductive choices and autonomy. Moreover, it may allow for earlier prenatal diagnosis and expectant management of genetic disorders.[26] Expanded carrier screening overcomes limitations of conventional carrier screening based on knowledge of ancestry and family history because all individuals are offered screening for a set of conditions regardless of race or ethnicity.[29] Although expanded carrier screening includes most of the genetic conditions recommended by current guidelines, they may include over a hundred genetic conditions, many of which are rare.[29] The expansive list of tested conditions pose implementation challenges due to the lack of standardization in panel composition, and pre- and post-test counseling and management.

Although ethical concerns have been raised, most can be addressed by best practices in implementation. Importantly, several health economics studies suggest that expanded carrier screening is more cost effective than conventional carrier screening in both cost per each affected birth avoided, and cost per life year gained.[15,16] Importantly, the majority of reproductive couples at risk of transmitting a serious condition to their offspring will alter their reproductive decisions,[14] suggesting that knowledge of the carrier status is of value to patients.

REFERENCES

1. Ioannides AS. Preconception and prenatal genetic counselling. *Best Pract Res Clin Obstet Gynaecol.* 2017;42:2-10. doi: 10.1016/j.bpobgyn.2017.04.003.
2. Centers for Disease Control and Prevemtion. ACCE model process for evaluating genetic tests. cdc.gov/genomics/gtesting/ACCE/. Accessed July 12, 2018.
3. Centers for Disease Control and Prevention. ACCE model list of 44 targeted questions aimed at a comprehensive review of genetic testing. cdc.gov/genomics/gtesting/acce/acce_proj.htm. Accessed July 15, 2018.
4. ACOG Committee on Genetics. Committee opinion No. 690: carrier screening in the age of genomic medicine. 2017;129(690):35-40. doi: 10.1097/AOG.0000000000001951.
5. Aetna. Genetic testing. aetna.com/cpb/medical/data/100_199/0140.html. Accessed June 22, 2018.
6. BlueCross BlueShield. Carrier screening for genetic disease. bluecrossnc.com/sites/default/files/document/attachment/services/public/pdfs/medicalpolicy/carrier_screening_for_genetic_diseases.pdf. Accessed July 17, 2018.
7. United Healthcare. Carrier testing for genetic diseases. uhcprovider.com/content/dam/provider/docs/public/policies/comm-medical-drug/carrier-testing-for-genetic-diseases.pdf. Accessed July 17, 2018.
8. Haque IS, Lazarin GA, Kang HP, Evans EA, Goldberg JD, Wapner RJ. Modeled fetal risk of genetic diseases identified by expanded carrier screening. *J Am Med Assoc.* 2016;316(7):734-742. doi: 10.1001/jama.2016.11139.
9. ACOG Committee on Genetics. Committee opinion No. 691: carrier screening for genetic conditions. *Obstet Gynecol.* 2017;129(3):e41-e55. doi: 10.1097/AOG.0000000000001952.
10. Department of Health and Human Services: Office of Inspector General. Memorandum report: coverage and payment for genetic laboratory tests, OEI-07-11-00011. oig.hhs.gov/oei/reports/oei-07-11-00011.pdf. Accessed July 18, 2018.
11. American Medical Association. Pathology/laboratory CPT code change applications: June 2017 CPT editorial panel meeing. ama-assn.org/sites/default/files/media-browser/public/physicians/cpt/molecular-path-public-listing-of-applications-june-2017.pdf. Accessed July 18, 2018.
12. American Medical Association. CPT editorial summary of panel actions: June 2017. ama-assn.org/sites/default/files/media-browser/public/physicians/cpt/june-2017-summary-panel-actions.pdf. Accessed July 18, 2018.
13. Quinn B. Discoveries in health policy. discoveriesinhealthpolicy.com/2018/05/brief-blog-myriad-acquires-counsyl.html. Accessed July 18, 2018.
14. Ghiossi CE, Goldberg JD, Haque IS, Lazarin GA, Wong KK. Clinical utility of expanded carrier screening: reproductive behaviors of at-risk couples. *J Genet Couns.* 2018;27(3):616-625. doi: 10.1007/s10897-017-0160-1.
15. Azimi M, Schmaus K, Greger V, et al. Carrier screening by next-generation sequencing: health benefits and cost effectiveness. *Mol Genet Genomic Med.* 2016;4(3):292-302. doi: 10.1002/mgg3.204.
16. Beauchamp K, Wong K, Lazzarin G, et al. Clinical impact and cost effectiveness of a 176 condition expanded carrier screen. Abstract 43, ACMG Annual Clinical Genetics Meeting 2018, Charlotte, NC. acmg.expoplanner.com/index.cfm?do=expomap.sess&event_id=12&session_id=7063. Accessed July 18, 2018.
17. Institute for Clinical and Economic Review. Assessing the effectiveness and value of drugs for rare conditions. icer-review.org/wp-content/uploads/2017/02/ICER_Assessing-the-Value-of-Drugs-for-Rare-Conditions_051017.pdf. Published 2017. Accessed July 18, 2018.
18. Stoll K, Resta R. Considering the cost of expanded carrier screening panels. *Genet Med.* 2013;15(4):318-319. doi: 10.1038/gim.2013.20.
19. Genpath. The pan-ethnic carrier tests from GenPath. genpathdiagnostics.com/womens-health/inherigen/. Accessed July 18, 2018.
20. Counsyl. Counsyl Complete. counsyl.com/provider/counsyl-complete/. Accessed July 18, 2018.
21. Lazarin GA, Detweiler S, Nazareth SB, Ashkinadze E. Genetic counselors' perspec-

tives and practices regarding expanded carrier screening after initial clinical availability. *J Genet Couns.* 2016;25(2):395-404. doi: 10.1007/s10897-015-9881-1.

22. Lazarin GA, Goldberg JD. Current controversies in traditional and expanded carrier screening. *Curr Opin Obstet Gynecol.* 2016;28(2):136-141. doi: 10.1097/GCO.0000000000000256.
23. Shiroff JJ, Nemeth LS. Public perceptions of recessive carrier testing in the preconception and prenatal periods. *J Obstet Gynecol Neonatal Nurs.* 2015;44(6):717-725. doi:10.1111/1552-6909.12764.
24. Holtkamp KCA, Mathijssen IB, Lakeman P, et al. Factors for successful implementation of population-based expanded carrier screening: Learning from existing initiatives. *Eur J Public Health.* 2017;27(2):372-377. doi:10.1093/eurpub/ckw110.
25. Holtkamp KCA, Lakeman P, Hader H, et al. Experiences of a high-risk population with prenatal hemoglobinopathy carrier screening in a primary care setting: a qualitative study. *J Genet Couns.* 2018:635-646. doi: 10.1007/s10897-017-0159-7.
26. Henneman L, Borry P, Chokoshvili D, et al. Responsible implementation of expanded carrier screening. *Eur J Hum Genet.* 2016;24(6):e1-e12. doi: 10.1038/ejhg.2015.271.
27. Grody WW, Thompson BH, Gregg AR, et al. ACMG position statement on prenatal/preconception expanded carrier screening. *Genet Med.* 2013;15(6):482-483. doi:10.1038/gim.2013.47.
28. Gronowski AM, Scott R, Caplan A, Nelson L. The ethical implications of preimplantation genetic diagnosis. *Clin Chem.* 2014;28:25-28. doi:10.1373/clinchem.2013.202515.
29. Edwards JG, Feldman G, Goldberg J, et al. Expanded carrier screening in reproductive medicine-points to consider. *Obstet Gynecol.* 2015;125(3):653-662. doi:10.1097/AOG.0000000000000666.
30. Arjunan A, Ben-Shachar R, Kostialik J, et al. Next-generation counseling: noninvasive prenatal screening results disclosure and management. *Preprints.* 2018:2018060284. doi: 10.20944/preprints201806.0284.v1.
31. Ready K, Haque IS, Srinivasan BS, Marshall JR. Knowledge and attitudes regarding expanded genetic carrier screening among women's healthcare providers. *Fertil Steril.* 2012;97(2):407-413. doi:10.1016/j.fertnstert.2011.11.007.
32. National Human Genome Research Institute. Genetic information nondiscrimination act of 2008. genome.gov/10002328/. Accessed July 18, 2018.
33. Nazareth SB, Lazarin GA, Goldberg JD. Changing trends in carrier screening for genetic disease in the United States. *Prenat Diagn.* 2015;35(10):931-935. doi: 10.1002/pd.4647.