A Clinician's Perspective on Expanded Carrier Screening: A Q&A With Jodi D. Hoffman, MD

JODI D. HOFFMAN, MD

Chief, Section of Genetics, Department of Pediatric Genetics
Associate Professor
Boston University School of Medicine

***AJMC®*: Would you discuss the evolution of genetic screening technology and how that trajectory has ushered in the development of expanded carrier screening technology?**

HOFFMAN: Tay-Sachs disease, the prototype disease for Jewish genetic screening, is carried by about 1 in 25 to 1 in 30 people of Ashkenazi Jewish (Eastern European) descent. In the late 1960s, due to the development of an enzyme assay to assess hexosaminidase A activity, screening for Tay-Sachs carrier status was introduced to the Jewish community to prevent the birth of more children with this fatal, neurodegenerative disease. The community united, encouraged by organizations like National Tay-Sachs and Allied Diseases to promote Tay-Sachs screening at community centers, synagogues, and medical offices, contributing to a tremendous reduction in Tay-Sachs disease. In the 1960s, there were about 60 children diagnosed with Tay-Sachs per year, and the Tay-Sachs ward in Brooklyn, New York, was full, with a waiting list. Due to the success of this screening program, there are now fewer than 5 affected children born per year in the Jewish community with this devastating disease. As the genes for other conditions seen in the Jewish community, such as Canavan disease and familial dysautonomia, were identified, testing ensued for these relatively common conditions, with carrier frequencies of about 1 in 40 for [each]. The American College of Obstetricians and Gynecologists (ACOG) adopted a policy of recommending screening for conditions for which there is a carrier frequency of 1 in 40 or more, [whereas] the American College of Medical Genetics and Genomics (ACMG) moved toward recommending screening for those conditions carried by 1 in 100 or more. This likely reflected the viewpoints of the different professional groups, in that most babies are born appearing normal and are later found to have rare conditions. Thus, the idea that screening is not needed for rare conditions, whereas geneticists tend to see rare conditions all the time, leaning toward screening for rarer conditions.

In the late 1980s, screening for the common mutations in the cystic fibrosis (CF) gene became available, and multiple professional organizations gave support to screening in the Caucasian community. Screening for hemoglobinopathies, such as sickle cell anemia and the thalassemias, [were] made available due to high carrier rates in those of African and Asian descent, respectively. As time went on, CF screening was recommended for people of all ethnic backgrounds. As the population of the United States has become less homogeneous and self-reported ethnic background is less likely [to be] accurate, screening panels have increased in breadth and depth, including more diseases and more mutations to allow for increased detection rates of carriers and carrier couples.

At first, larger screening panels were more time intensive, using several individual polymerase chain reaction [PCR] assays to genotype for the most common mutations seen in the Ashkenazi Jewish population. As more genes for Jewish genetic diseases were identified, bead assays were made available to screen for the mutations most commonly seen in in this population. A technology statement was released by the ACMG [that provided] information regarding screening for 8 conditions, all of which were available via one bead assay. Soon, labs were competing to provide larger panels. The Jewish community had embraced the option to screen prior to reproduction to allow for the greatest number of reproductive options, at first via PCR based assays and larger bead technologies; soon [after], via chip technologies. This broader

screening became standard among the most religious groups and was highly encouraged in other denominations. Jewish genetic screening programs developed along with support groups, each with members with different rare diseases. Many groups lobbied for the addition of specific diseases. Whereas the ACMG had recommended screening for conditions that had high detection rates and carrier frequencies of at least 1 in 100, screening tests were eventually developed for those with either criteria, increasing the number of diseases included. Technology shifted to next-generation sequencing of entire genes, allowing for high detection rates in people of all backgrounds.

***AJMC®*: How is clinical utility of genetic carrier screening defined and measured, and how important is context when it comes to that definition and measurement?**

HOFFMAN: The clinical utility of CF screening, as well as sickle cell screening, have been assessed for detection rate and cost and [have been] adopted by healthcare providers, as well as insurers. Screening for large panels was assessed in terms of cost-effectiveness. One article cited that the price point at which screening for rare diseases becomes cost-effective is about $350. As CF screening, along with hemoglobinopathy screening, [has] cost [$350] until quite recently, newer technologies [that] allow for greater than 90% detection of many recessive and X-linked disorders using 1 test have become standard of care for many providers and the [expected method] of many couples.

***AJMC®*: Can you shed light on the variety of panels available, and how they can be differentiated, particularly from a payer perspective?**

HOFFMAN: There are many different panels with overlapping inclusion of diseases. As the ACMG and ACOG have issued statements as to which conditions are important for screening the general population—CF and, more recently, spinal muscular atrophy—and specific ethnic groups such as those mentioned above, a panel that includes at least these conditions is optimal. [Because] most people are no longer aware of their true ethnic makeup, a panel including all of these conditions avoids false reassurance with regard to reproductive risk. As technology allows for complete sequencing, as well as deletion/duplication assessment, at the same or lower cost than previous technologies, which provided [just] genotyping for a limited set of mutations, sequencing has become standard of care.

***AJMC®*: How does panel constitution affect the relevance of carrier screening results?**

HOFFMAN: As noted previously, genotyping tends to be ethnic specific, looking [just] for mutations seen commonly among people of a specific background, whereas sequencing detects all known mutations for a given condition. One major concern is that some ethnic-based panels still exist, and providers are not aware that the mutations present on the panel are relevant only for a certain population. For instance, genotyping for the most common mutations in the gene for Tay-Sachs detects over 90% of Ashkenazi Jewish mutations but closer to 60% of the mutations seen in people from other backgrounds. Again, screening for a limited number of mutations is likely to provide false reassurance to those screened unless complete sequencing and/or enzyme analysis is performed.

***AJMC®*: Can you discuss recent advances in sequencing methodologies and how they have—or have not—affected the use of carrier screening technology in prenatal care?**

HOFFMAN: Next-generation sequencing has been used for quite some time to allow for complete sequencing of multiple recessive conditions at the same time. Due to its rapid processing time and low cost compared [with] PCR, this technology has been readily adopted by molecular labs. Whole exome sequencing (WES) is aimed at over 20,000 genes, many of which do not yet have known clinical relevance and [involve] conditions so rare that little is known about the pathogenicity of single-base pair changes, although standard variant classification can be used to predict pathogenicity in some cases. It seems that WES in the screening sphere is still new and not yet adopted by most in clinical practice and may produce more data than needed for the screening process at this time.

***AJMC®*: What are some of the challenges associated with carrier screening and its use, and how can they be addressed?**

HOFFMAN: Carrier screening is largely unregulated and not standardized at this time. There is no specific time in life or specific type of specialist to note the need for screening prior to family planning. Screening labs aim to include all those conditions recommended by professional organizations: use technology with a high detection rate, [have] consistent variant classification, [employ] clear reporting, and [have the] ability to provide results rapidly to allow a carrier couple the broadest choice of reproductive options, preconceptionally or prenatally. As each lab may include many of the same conditions, some conditions are not included by each lab, due to different professional interpretations of which conditions are serious enough to [affect] reproductive decision making and which screening tests have been optimized to produce high enough detection rate to meet the standards of that lab. Some genes have pseudoalleles, or regions that are hard to sequence, decreasing sensitivity. Some providers do not understand the difference between genotyping and sequencing or the need to do partner follow-up screening with a lab that provides the greatest sensitivity for the condition in

question. Occasionally, 1 member of the couple has [had] screening at 1 lab and the other at another lab, and [they] do not realize that their testing did not include all of the same conditions.

Producing a clear set of guidelines regarding [at] what time of life this topic should be addressed; offering screening prior to reproductive planning, if possible, and [during pregnancy] if preconception screening has not occurred; developing a minimum list of conditions to be screened for and updating this list over time, [along with] the expectations for sensitivity for all screening tests; and providing a resource for patients that is clear, easy to understand, and presented in different languages and [to] people of different beliefs. Some of this work was done in a joint statement by many of the professional organizations in 2015,[1] but more work is needed to optimize the process.

***AJMC®*: Can you discuss the concept of variant curation and the broader idea of how carrier screening results are directed toward patients?**

HOFFMAN: As opposed to diagnostic testing, in which variants of uncertain significance for a gene relevant to the condition at hand are important, screening is aimed at providing clear reproductive risks for carrier couples. Only those mutations that are known to be pathogenic via literature and ACMG variant curation guidelines are reported out. Due to the historical nature of screening for Tay-Sachs via enzyme, studies are ongoing to correlate variants in the *HEXA* gene with enzyme activity. To date, no variants of uncertain significance have been found to result in hexosaminidase activity in the carrier range, reassuring molecular labs that DNA sequencing has as high a level of sensitivity as the traditional enzyme activity. As the hemoglobinopathies have traditionally been screened for via hemoglobin electrophoresis and now [that] these conditions are included on many expanded panels, such correlations should also be available for these conditions. By moving toward 1 test to detect carriers for conditions [that] previously required 3 separate methodologies—molecular for CF; enzyme for Tay-Sachs; electrophoresis for hemoglobinopathies—cost savings are likely. Most patients would like to know as much information as possible when planning a pregnancy, but uncertain information is not welcome by most couples.

***AJMC®*: How would you assess the overall significance of prenatal genetic carrier screening and the importance of access to the technology?**

HOFFMAN: Preconception and prenatal carrier screening are important [for] providing couples with information that allows for the birth of healthy children or for the education and preparation of parents who choose to proceed with a natural pregnancy and/or continue an affected pregnancy. For those whose moral and religious values allow the use of adoption or reproductive technologies, families can avoid the pain and suffering and economic hardships of having a child with a serious genetic condition that alters quality of life and/or length of life. For those who choose to reproduce naturally, early identification of conditions for which pregnancy or neonatal management can be altered allows for improved outcomes. For instance, if a family knows that they have a 25% chance of having a child with a metabolic condition that requires restricted protein from birth, hyperammonemia, seizures, and resultant intellectual disability may be prevented [by] assuming the baby is affected until testing is completed. For a child expected to have a severe hemophilia, special care can be taken in the newborn period to prevent bleeding due to circumcision or other procedures. Overall, whether the information is used to allow for the birth of unaffected children or affected children with optimized care, the health and well-being of families are improved due to availability of carrier screening.

REFERENCE

1. Edward JG, Feldman G, Goldberg J, et al. Expanded carrier screening in reproductive medicine—points to consider: a joint statement of the American College of Medical Genetics and Genomics, American College of Obstetricians and Gynecologists, National Society of Genetic Counselors, Perinatal Quality Foundation, and Society for Maternal-Fetal Medicine. *Obstet Gynecol.* 2015;123(3):653-662. doi: 10.1097/AOG.0000000000000666.