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CURRENT STATE OF DOR YESHORIM, EXPANDED CARRIER, AND NEWBORN SCREENING: BENEFITS AND LIMITATIONS

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Abstract
Availability and accessibility of preconception and prenatal genetic carrier and newborn biochemical and genetic screening have grown exponentially over the past 2 decades and as such, it is challenging for clinicians to keep pace. Although genetic counseling or genetic consultation should be offered to all expectant and new parents for prenatal screening decisions and positive results, benefits and limitations of these tests and results must be known and familiar to perinatal and pediatric clinicians. A brief historical overview of Dor Yeshorim, preconception and prenatal expanded carrier, and newborn screening is presented, followed by discussion about the conditions screened and considerations surrounding the benefits and limitations of these tests in the practice setting.

Key words: Carrier screening; Genetic; Neonatal; Prenatal diagnoses; Prenatal screening; Screening; Testing.

As genetic testing methodologies such as next-generation sequencing have become more readily available and declined in cost, a deeper understanding of the various prenatal and postnatal genetic screening methods, the conditions screened, and their benefits and limitations is critical. Preconception and prenatal genetic carrier screening are intended to identify individuals or couples at risk to have a child with autosomal recessive and/or X-linked genetic disorders, whereas newborn screening targets presymptomatic newborns with congenital or inherited disease to prompt early diagnosis and lifesaving or life-changing treatments. Professional organizations such as the American College of Obstetricians and Gynecologists (ACOG), American College of Medical Genetics and Genomics (ACMG), and National Society of Genetic Counselors (NSGC) recommend offering prenatal carrier screening based on disease severity, race or ethnicity, prevalence/carrier frequency, detection rates, and residual risk.

Testing beyond prenatal cystic fibrosis, sickle cell disease, and "Jewish panel" screening; maternal serum analytes, fetal ultrasound, and noninvasive prenatal testing is reviewed to provide an overview of more complex testing available in the preconception, prenatal, and postnatal settings: Dor Yeshorim compatibility genetic screening, expanded genetic carrier screening, and newborn screening. A historical overview of each of these tests and systems including the current conditions screened is presented. Benefits and limitations of these screening tests and programs, and overlap and lack of the conditions screened to ensure clinicians across all levels of perinatal and pediatric practice remain abreast of and can appropriately provide information and counseling about prenatal and postnatal genetic and congenital disorder screening, are covered.

> Prenatal expanded carrier screening is recommended for individuals or couples seeking prenatal care.

Dor Yeshorim

Dor Yeshorim (also known as the Committee for Prevention of Jewish Genetic Diseases) is a nonprofit, international organization operating in 11 countries that provides confidential premarital compatibility genetic screening. It emerged from the increased risk for recessive disease initially among individuals of Ashkenazi Jewish descent (Shi et al., 2017), but has since expanded to other Jewish populations. Information gleaned about Dor Yeshorim and its current screening panel and services provided was retrieved from the Dor Yeshorim website. The organization is supported and endorsed by rabbinical authorities and the medical community, and its mission is to eliminate debilitating autosomal recessive genetic disease and associated morbidity, mortality, and stigma among Jewish families. Dor Yeshorim is also actively engaged in genetic disease and prevention of genetic disease research and offers counseling, education, and support to families suffering from genetic illness (Dor Yeshorim, n.d.).

Because of strict religious practice adherence, Dor Yeshorim originated within the Hasidic Jewish community, but has since expanded to broader Orthodox Jewish communities. Screening started in 1983 with Tay–Sachs disease and over the past 3 decades, has expanded to include other conditions such as cystic fibrosis, familial dysautonomia, and Canavan disease. Diseases are carefully reviewed and scrutinized before inclusion and are added based on recommendations from the ACMG, Israeli Health Ministry, and Dor Yeshorim Medical Advisory Board. Dor Yeshorim is committed to testing only for common, incurable autosomal recessive diseases that cause severe health problems, are fatal, and for which there are reliable testing methods with definitive carrier status results. Unlike other commercially available genetic tests, samples collected are anonymized. Results are never disclosed, but through the tradition of Jewish matchmaking, carriers of the same genetic condition are not partnered (Dor Yeshorim, n.d.).

This voluntary testing is available to individuals of Jewish ancestry and those partnering with individuals who have converted to Judaism and are of non-Jewish origin. As of July 2022, there are several panels available. The standard panel tests for 52 conditions (Dor Yeshorim, n.d.) for which the incidence among individuals of Jewish background differs. An overview of types of Jewish ancestry and population differences is provided in Table 1. In addition to the standard panel, Dor Yeshorim offers a hearing panel intended to reduce the risk of inherited hearing loss. This panel screens for 22 different types of genetic hearing loss (some associated with blindness) including Pendred syndrome and various types of Usher syndrome. There is an advanced panel that screens for an additional 50 mild and newly discovered genetic diseases, the names of which are not available on the website (Dor Yeshorim, n.d.).

Benefits and Limitations

Although Jewish law is nuanced, strict Orthodox Judaism opposes elective termination of pregnancy unless the life of the mother is at risk. However, in pregnancy scenarios where there are risks to the health of the fetus and/or mother, a competent Rabbinic authority may be asked to guide decision-making with the Orthodox Jewish couple. Dor Yeshorim allows couples to be matched based on their genetic profile to eliminate the risk of debilitating or fatal genetic disease. Screening through Dor Yeshorim allows Jewish couples to avoid marriages (and as such conception) between "carriers" and know associated risk for conditions screened. If a couple is identified to be at risk for one of these conditions, known preconception risk allows interested couples to pursue preimplantation genetic diagnosis, often approved by Jewish law (Dor Yeshorim, n.d.).

Dor Yeshorim is dedicated to screening for autosomal recessive Jewish genetic diseases associated with

significant morbidity and mortality (Dor Yeshorim, n.d.). Screening is often performed during high school years, therefore couples who are currently pregnant underwent the screening available at that time (approximately 10 conditions), not the more expanded panels being offered today. Because of these gaps, a Jewish couple who received Dor Yeshorim screening should also be offered routine prenatal expanded carrier screening consistent with current ACMG and ACOG recommendations. When offered with cultural humility and respect, couples will often be receptive to genetic testing information and counseling.

Prenatal Expanded Carrier Screening

Genetic carrier screening and counseling have been available in prenatal settings since the 1970s, and by the late 1990s, professional organizations such as ACOG, ACMG, and NSGC recommended screening for all individuals or couples seeking prenatal or preconception care. In the past, genetic carrier screening was targeted to individuals based on racial or ethnic backgrounds, cultural customs that limit random mating, and personal or family history of a known or suspected inheritable disease. Examples of conditions screened based on these criteria include hemoglobinopathies and thalassemias among non-White and Mediterranean populations; "founder effect" (ancestry-based) screening for Tay–Sachs disease among individuals of Ashkenazi Jewish, French Canadian, and Cajun descent; and cystic fibrosis among non-Jewish White individuals.

As advances in high-throughput molecular technology, panel testing, and turnaround time have improved, the cost of testing has declined, and as our population has become more diverse, the number of conditions for which couples can be screened has increased. These factors have allowed screening to extend to conditions with a very low carrier frequency, milder phenotypes (Mastantuoni et al., 2018), and beyond "high risk" ethnic groups to provide more equitable screening (Gregg et al., 2021). Even with the largest of panel tests, however, there are limitations to screening.

Currently, there is no industry standard for carrier screening and the number of conditions screened differs between laboratories. Panels, testing methodology, and reporting practices differ and change over time. Many companies offer expanded carrier screening and have developed their own list of disorders. Therefore, prenatal screening lacks uniformity. Some panels test for only a few conditions, whereas others test for several hundred (Table 2). At present, there is an almost al a carte approach to the panels offered and conditions screened.

Currently, ACOG (ACOG, 2017a, 2017b) and ACMG (Gregg et al., 2021) recommend inclusive (pan-ethnic) carrier genetic screening for our diverse populations for all pregnant persons for cystic fibrosis and spinal muscular atrophy. Fragile X syndrome premutation carrier screening is recommended when the maternal family history suggests intellectual disability or fragile X syndrome or related disorders (ACOG, 2017a, 2017b; Gregg et al., 2021). A complete blood cell count and red blood cell indices are recommended to assess for hemoglobinopathies, and hemoglobin electrophoresis should be performed based on suspicion and ethnicity (African, Mediterranean, Middle Eastern, Southeast Asian, or West Indian descent). Reproductive partners should be offered screening for autosomal recessive conditions simultaneously or based on result of the expectant patient.

Because of the changing face of genetics and genetic testing, Gregg et al. (2021) and colleagues from ACMG recommend a 4-tiered approach to carrier screening based on ACMG and ACOG (2017a, 2017b) guidelines. Tier 1 entails an ethnic and population-neutral approach when carrier screening for cystic fibrosis and spinal muscular atrophy. Screening for other conditions should be based on a risk assessment elicited by a personal or family history, laboratory testing, and imaging. Tier 2 (includes Tier 1)

TABLE 1. MAJOR JEWISH ANCESTRAL GROUPS

Ethnic Jewish Group	Regions	Overview
• Ashkenazi Jews (Eastern [European] Jews)	• Central and Eastern Europe	• Jews of Central Europe and the Jewish diaspora • Largest Jewish group (2/3 of Jews are Ashkenazi) • Genetically homogenous with high burden of disease because of founder effect
• Sephardi Jews (Southern Jews)	• Southwestern Europe, North Africa, the Middle East, the Mediterranean, and Spain	• Jews of the Iberian Peninsula and the Spanish diaspora • Practice Judaism with a few variations • Tend to observe more orthodox customs
• Mizrahi Jews ("Oriental" Jews)	• North Africa, the Middle East, and Central Asia	• Jews of Babylonian and Persian heritage • Practice Jewish and regional customs and clothing
• Ethiopian Jews	• North Africa (Ethiopia)	• Unique branch of Judaism • Rely on oral traditions because of nomadic lifestyles among most Ethiopians

Note: This table shares the ethnic and racial diversity among Jews which contribute to their genetic differences. Compiled from: https://www.myjewishlearning.com/article/sephardic-ashkenazic-mizrahi-jews-jewish-ethnic-diversity/

recommends screening for conditions with a severe or moderate phenotype and carrier frequency of at least 1/100. Cystic fibrosis and spinal muscular atrophy also meet these criteria. Tier 3 (includes Tier 2) recommends all pregnant individuals and couples planning a pregnancy be offered carrier screening for autosomal recessive conditions with an incidence of ≥1/200 and disorders that are X-linked. Screening for autosomal recessive conditions in reproductive partners may be considered when performed in parallel with their partner. Tier 4 (includes Tier 3) incorporates genes with a carrier frequency <1/200 but for which the natural history of the disease (including genotype–phenotype correlation) is less known. According to ACMG, this tier of testing should be reserved for consanguineous pregnancies (second cousins or closer) or if there is a significant family or medical history that supports testing (Gregg et al., 2021).

Benefits and Limitations

As is its purpose, preconception or prenatal expanded genetic screening can identify at-risk couples and pregnancies allowing for improved autonomy for current and future reproductive decision-making. Although valid attempts have been made, the depth and breadth of carrier screening remain inconsistent and as such, debate and controversy about the clinical utility and application of expanded carrier screening still exist (Guo & Gregg, 2019; Kraft et al., 2019).

Although the tiered approach to prenatal genetic carrier screening is helpful, the decision about whether a patient receives targeted or expanded carrier screening remains a decision between the patient, partner, and provider. If it is decided to move forward with screening, numerous laboratories offer expanded carrier screening services which allows multiple avenues and approaches for screening interested patients. Companies offer various testing methodologies that may include a combination of Sanger sequencing, enzyme analysis, capillary electrophoresis, multiplex ligation-dependent probe amplification assay, single-nucleotide variants, and copy number variants. Tests viewed as routine, especially due to family history, by health insurance companies may be covered at no cost. Navigating genetic testing costs and insurance coverage, however, may be confusing and there may be an associated cost depending on the insurance plan. Although most companies offer self-pay options, payment plans, and other options such as sliding scales based on income, prenatal expanded carrier screening is not currently a routine part of prenatal care.

Specific to the test itself, most companies that offer expanded carrier screening report only pathogenic or likely pathogenic genetic variants (at the time of screening), and variants of uncertain significance (those not known to be either pathogenic or benign) are not reported. Screening may not include all variants. Some may not be detectable by the technology used or are technically difficult to assess. Laboratories may differ in how they choose to classify variants, and testing can also miss mosaicism (Gregg et al., 2021; Veneruso et al., 2022). Furthermore, testing includes disorders with varying ages of onset, severity, and penetrance (Gregg et al., 2021), which can present challenges for reproductive decision-making. Although a negative test reduces the chance of having an affected child, it does not eliminate all risk.

TABLE 2. EXPANDED CARRIER SCREENING PANELS AND NUMBER OF DISORDERS/GENES OFFERED

Company and Panel	Number of Disorders/Genes
QHerit® Expanded Carrier Screen	22 disorders
Inheritest® 100 PLUS Panel Disorders	>100 disorders
Natera™ Horizon™	up to 274 disorders
Inheritest® 500 PLUS Panel Disorders	>500 genes
Sema4 Elements® ECS	up to 502 genes
Invitae Comprehensive Carrier Screening	up to 569 genes

Note: The table lists a sample of several panels and compiled from information available on the respective company websites. Retrieved April 21, 2023, from: https://testdirectory.questdiagnostics.com/test/test-guides/TS_QHerit/qherit-expanded-carrier-screen; https://womenshealth.labcorp.com/providers/carrier-screening/inheritest-panels/inheritest-100-plus-panel-disorders; https://www.natera.com/wp-content/uploads/2021/01/Horizon-Patient-Brochure-English.pdf; https://www.labcorp.com/tests/481893/inheritest-500-plus-panel; https://cdn1.sema4.com/wp-content/uploads/Sema4-Elements-Carrier-Screening-Panel-Guide.pdf; https://www.invitae.com/en/providers/test-catalog/test-60100

Based on panel differences, it is imperative clinicians carefully review the conditions included in each panel, the date performed, and seek information about identified variants and their pathogenicity which can evolve over time. As panels continue to grow, it is important to educate and counsel individuals and couples about the limits of this testing. Clinicians must also provide precise education and preparation to patients so they are aware the more conditions screened, the more potential variants in the couple will be identified. Additional genes and genetic referral may be warranted should the family history cause concern. It is important to reoffer carrier screening if a reproductive partner has changed.

Newborn Screening

Newborn screening was first initiated in the 1960s when Dr. Robert Guthrie developed a bacterial inhibition assay, filter (Guthrie) paper blood spot test to diagnose infants with an inborn error of metabolism called phenylketonuria. There was little expansion of biochemical screening over the next 3 decades but in the late 1990s and early 2000s, high-throughput technologies such as tandem mass spectrometry and accessibility followed by availability and affordability of gene sequencing have allowed newborn screening to grow exponentially. Nonbiochemical newborn hearing and critical congenital heart disease screening have also been incorporated into this robust system.

CLINICAL IMPLICATIONS

- Clinicians in the preconception, prenatal, and early postnatal settings must remain abreast and informed of current screening guidelines and practice and know and understand the similarities and differences between Dor Yeshorim, preconception and prenatal expanded genetic carrier screening, and newborn screening respective to their practice setting.
- Dor Yeshorim is guided by the American College of Medical Genetics and Genomics, Israeli Health Ministry, and Dor Yeshorim Medical Advisory Board and provides confidential premarital compatibility genetic screening to individuals of Jewish descent.
- Prenatal expanded carrier screening is recommended for individuals or couples seeking prenatal care and guided by professional organizations such as the American College of Obstetricians and Gynecologists, American College of Medical Genetics and Genomics, and National Society of Genetic Counselors.
- Expanded carrier screening is available to at-risk couples as part of preconception counseling and care.
- The American College of Obstetricians and Gynecologists and American College of Medical Genetics and Genomics recommend inclusive genetic carrier screening for cystic fibrosis and spinal muscular atrophy, fragile X syndrome premutation carrier screening based on family history, and complete blood cell count and red blood cell indices based on family history, disease suspicion, and/or ethnicity.
- Reproductive partners should be offered screening for autosomal recessive conditions simultaneously or based on results.
- Preconception and prenatal expanded carrier screening do not test for all genetic conditions or identify *de novo* variants in offspring.
- Clinicians should recognize there is overlap and lack of overlap between panels and as such, understand the benefits and limitations of these tests and be prepared to answer questions about these tests.
- In the United States, newborn screening is guided by the Recommended Uniform Screening Panel and its purpose is to provide early/presymptomatic diagnosis of conditions that might otherwise go unnoticed.
- Whether Dor Yeshorim or expanded carrier screening, these tests do not replace newborn screening, and newborn screening does not diminish the benefit of preconception/prenatal carrier screening.
- Genetic counseling about the results should be provided based on the clinician's level of practice. In some cases, referral may be necessary.
- It is important to make sure patients understand the findings and there is no misinterpretation of results.
- Confidentiality of all genetic test results should be maintained.

The purpose of newborn screening is to prompt early and often presymptomatic diagnosis of conditions that might have otherwise gone unnoticed in an asymptomatic newborn to decrease morbidity and mortality and improve neonatal outcomes. Although some have proposed whole exome and genome sequencing for newborns, currently, there are more than 60 disorders for which newborns can be screened. The conditions screened on the panel, however, vary by state.

Although countries outside the United States offer universal (national panel) newborn screening, the United States does not. This may be perceived as a disadvantage, however, as per an industry overview of newborn screening across Europe (Wilsdon et al., 2021), information from 30 countries reveals significant differences in the number of conditions offered through national panels. Italy, Portugal, and Austria screen for the largest number of conditions (>25) whereas Romania and Cyprus test for only two. France and UK national panels test for <10 conditions (Wilsdon et al., 2021).

There is a national committee that recommends the conditions that should be considered for inclusion in newborn screening. The intent is to standardize screening and minimize screening differences between states. The Advisory Committee on Heritable Disorders in Newborns and Children meets regularly to review and vet nominated conditions and, based on those reviews, approve or deny screening recommendations to move toward a uniform screening panel. If approved, the committee submits its recommendation to the Secretary of the Department of Health and Human Services who determines if the condition will be added to the recommended uniform screening panel (RUSP; Advisory Committee on Heritable Disorders in Newborns and Children, 2023).

The RUSP provides a model for newborn screening to which states refer for guidance and includes core and secondary conditions. As of January 2023, the core panel includes 9 organic acid disorders, 5 disorders of fatty acid oxidation, 7 amino acid disorders, 2 endocrinopathies, 3 hemoglobinopathies, and 10 other conditions, whereas the secondary panel includes another 6 organic acid disorders, 8 disorders of fatty acid oxidation, 8 amino acid disorders, 1 hemoglobinopathy, and 3 other conditions.

Although all states screen for core conditions listed on the RUSP, newborn screening is state-based. Each state determines what should be included based on patient population diversity, anticipated population and disease prevalence, incidence rates, detection rates, treatment options, and infrastructure and financial considerations. Even when a condition has been added to the RUSP and state screening, not all states can begin screening immediately and not all states screen for secondary (disorders that may be detected in the differential diagnosis of a core condition) or newly added conditions.

Benefits and Limitations

Newborn screening is considered an exemplary and extremely successful model of public health in preventing

morbidity and mortality associated with symptomatic and late diagnosis and treatment of newborns and children that may otherwise go unnoticed and experience irreparable damage (Institute of Medicine Roundtable on Translating Genomic-Based Research for Health, 2010). As it is often stated, "newborn screening saves lives."

As newborn screening varies from state to state and country to country, clinicians must know what conditions are screened in their state or country and continue to follow those changes. In the United States, neighboring states may have different screening panels. Knowing the state where an infant was born can help primary and specialty care clinicians understand whether a symptomatic infant or child was screened.

The accuracy and reliability of testing have improved over time, and for some conditions, reflex DNA testing/gene sequencing has improved specificity. Newborn screening, however, remains a screening (not diagnostic) test. Newborn biochemical screening cut-off values are set conservatively with a goal not to miss any affected newborn, which results in false-positive results. Some newborns who are disease carriers or have no disease may be identified through screening which can raise anxiety levels in parents. These false-positive screens, however, can prompt genetic carrier testing for parents to determine the risk of having an affected child in the future. Because this is a screening test, it is important to note, if there is an index of suspicion an infant or child has a condition on the newborn screening panel, confirmatory testing for that condition should be ordered.

Like prenatal expanded carrier screening, newborn screening has grown to include conditions with a mild variable phenotype or for which there is no currently available treatment or cure. Although most programs base their approach to screening on the Wilson and Jungner (1968) criteria, availability of testing for conditions with a lack of available treatment or cure has become controversial. Diagnosis of a condition for which there is no effective treatment or cure may not positively influence the health of the newborn, however, may provide reproductive risk information to the parents. Another debate is whether adult-onset conditions should be screened for and identified in the newborn period. Although this remains controversial, newborns found to be affected with juvenile- and adult-onset conditions can trigger genetic testing of other family members which can help improve quality of life and in some instances, save lives.

Conclusion

As the availability and disorders screened within the Dor Yeshorim, prenatal expanded carrier screening, and newborn screening panels are expanded, clinicians must remain current and well-informed of the conditions screened, and the benefits and limitations of the testing and test results. Prenatal genetic carrier and newborn screening were founded with the purpose of the prevention and diagnosis of severe, infantile-, or childhood-onset disorders to optimize early and more successful treatment and outcomes and identifying genetic disease carriers to allow individuals to make autonomous reproductive decisions. It does not, however, test for all genetic conditions or identify *de novo* (spontaneous or new) variants in offspring. It is also important to note, Dor Yeshorim and expanded carrier screening do not replace newborn screening and newborn screening does not diminish the benefit of prenatal carrier screening (ACOG, 2017a, 2017b). Parents must receive counseling about the similarities and differences between various screening panels and why their newborn may screen positive for a condition for which they were not aware they were at risk to conceive.

With technological advances, conditions screened have and continue to migrate from the intended purpose of screening as outlined by Wilson and Jungner (1968) and at present, insurance coverage for prenatal expanded carrier screening is not universal. Therefore, it is imperative individuals receive pre- and postscreening carrier screening by a knowledgeable and trained health care professional to ensure there is no misinterpretation of test results while maintaining the privacy and confidentiality of those results. Counseling must also include information about the implications of genetic testing including the Genetic Information Nondiscrimination Act (2008), which makes it illegal for health insurance companies to require individuals to disclose genetic test results or use those results to make decisions about coverage, rates, or preexisting conditions and for employers with greater than 15 employees to discriminate based on genetic information. Although some states have laws that offer additional protections, this act does not protect for preexisting genetic conditions diagnosed and manifest surrounding life, long-term care, or disability insurance (Genetic Information Nondiscrimination Act, 2008; National Human Genome Research Institute, 2022). Clinicians must remember carrier screening will not identify all at-risk individuals and therefore individuals must receive counseling on residual risk. If a condition is suspected in the prenatal or postnatal setting, genetic consultation and confirmatory testing for the condition should be ordered. Screening for any or all conditions is optional, and after counseling, an individual or couple may decline any or all screening tests for themselves and/or newborn. ✣

Acknowledgment

The author thanks Molly Ciarlariello, MS, LCGC, and Sara Welner, MS, LCGC, for their careful and thoughtful review and critique of this manuscript.

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The author declares no conflicts of interest.

DOI:10.1097/NMC.0000000000000939

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